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HOWARD ATWOOD KELLY*

Presidential Address

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ONE cannot assume the presidency of this Society composed, as it is, of one's best friends and most respected colleagues without a feeling of great humility. One is especially humbled when he contemplates the illustrious men who have preceded him as president of this organization. I look back at one of our former presidents with special pride and affection and I am sure many of the older Fellows will join me in this fond memory. I refer to the first Professor of Gynecology of the Johns Hopkins University, Dr. Howard Atwood Kelly. To most of the present Fellowship of this Society he is only an illustrious name but we all owe much of our training in modern gynecology to him whether or not we are conscious of it.

"Accordingly as we remember others so those yet to come will remember us. If we live only for the present and for our own age and reject the past because of imperfections, so in turn will we ourselves as surely be forgotten and despised as the centuries roll over our dust." These are the words of Howard Kelly spoken in 1912, to this Society in his introductory remarks as he presented his Presidential Address on "The History of Vesico-Vaginal Fistula." It would seem from these words that he had some intimation that he, too, was making gynecological history as did the illustrious Simms, Emmett, and others, whose work he was reviewing.

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It is not an easy task, within the time allotted me, to give you a comprehensive picture of the life of such a colorful and versatile man as Howard Kelly, but I shall try to give you a very brief sketch of the many facets of this remarkable character.

Dr. Kelly was born in Camden, New Jersey, on Feb. 20, 1858, the son of Henry Kuhl and Louisa Warner Kelly. His mother, the daughter of an Episcopal minister, was a deeply religious woman and it was from her that he apparently acquired his early training in religion of the strictest fundamentalist type, which he professed openly and worked at ardently throughout his life. His father was a successful man of affairs and served in the Union Army. His great-great-grandfather, Michael Hillegas, was the first treasurer of the United States.

At the age of 9, Howard Kelly was entered as a pupil in Faire's Classical Institute. There he received excellent training in the classics. Perhaps this early training accounted for his ability to write, speak, and read German, French, and Spanish easily and correctly. After his school days he became sufficiently familiar with Greek and Hebrew to read the Bible in these languages. He was wont to keep his linguistic talents to himself but on occasion amazed the staff when he displayed them. Dr. Casler relates how on one morning there was a visiting nurse from Athens, Greece, in the operating room. When she was introduced to Dr. Kelly, he conversed fluently with her in her native tongue.

While reviewing his own life at the banquet given for him in 1933, Dr. Kelly said, "I wanted first to be a naturalist and went into medicine as a close ally. Going through the medical school at the University of Pennsylvania, I got a bad case of insomnia, and broke down, shortly before graduation, mostly from overwork. I went out to Colorado in 1879, batching it in Colorado Springs and then went out onto the O-Z Ranch in Elbert County as a cowboy.

"I gave thanks when I returned to Philadelphia in 1882. My real education came in the dispensaries and wards of the Episcopal Hospital among the Kensington folk who trusted me and repaid my poor efforts with a warm friendship which continues today. In this atmosphere of trust and affection, I felt I had found richer rewards than even the greatest of the sciences could bestow.

"After my residency in the Episcopal Hospital, it seemed better to locate right there in Kensington, where work was waiting, than to settle down assisting the older doctors. The patients were poor, some of them lived in near-by Louse Harbor! But they let me do things which would not have been possible down town.

"My old friend and teacher, Dr. William Goodell, was rather critical, fearing I was getting too bold."

But Dr. Kelly was encouraged in his pioneer efforts at surgery by such men as Agnew, Horatio Wood, William Pepper, and Osler, whom he called frequently in consultation.

He continues: "After my apprenticeship in the big Philadelphia mill area, and as associate professor at the University of Pennsylvania, came the call to Hopkins to join the splendid group, ready to venture new things in medicine both in its practice and teachings, with Welch and Osler, Halsted and Hurd, in 1889."

Thus at the age of 31 did the youthful-appearing "Kensington Colt" come to Hopkins as the first professor of gynecology and obstetrics and director of these departments. His youthful appearance was the occasion of many practical jokes, especially by Osler who took pleasure in portraying Dr. Kelly to his patients as a man of mature age and dignity. Then he would usher in the boyish, smooth-shaven Kelly and delight in watching the patient's reaction.

On one occasion Osler asked Kelly to cystoscope one of his patients, which he did by the air method. As Dr. Kelly put his eye to the cystoscope the patient suddenly sneezed, allowing a blast of urine to hit him in the face. Kelly immediately picked up the patient's history and wrote: "Dear Osler: All I know about your patient is that her urine is salty."

Immediately on the opening of the Johns Hopkins Hospital, Kelly established the long-term residency training in Gynecology, with Hunter Robb as the first resident. Judging by the quality of his several residents we may wonder whether this was not his greatest contribution to his specialty. A list of his residents would include many of the fellows in this Society of that era. Kelly's postgraduate discipline, by means of the long-term residency, was an entirely new concept in surgical training at that time. Each year the assistant residents were given increasing responsibility in the care of patients and in the operating room. Surgery upon the ward patients was done almost exclusively by the resident and his assistants, subject to consultation and help when necessary by the senior staff. Kelly was most kind and considerate in his relation to his house staff, treating the younger men as friends and younger brothers, rather than assistants. Nevertheless, he gave them heavy clinical responsibility and insisted that they fulfill their obligations. When asked on one occasion why he did so much for his house staff he replied: "When I was resident in a Philadelphia hospital, the head of the surgical department wanted to do everything himself, and when I amputated a finger upon one occasion, the surgeon reported me to the trustees for over-stepping my authority. I made up my mind, right then and there, that if I ever were head of a surgical department, my men would be given every opportunity." How long it has taken for Dr. Kelly's idea of real residency training with increasing responsibility year by year to be generally accepted in this country, and how much the creation of more residencies in fact as well as in name would do for the training of gynecologists!

We have set up standards of training in gynecology today, but to what avail if first-class residency training cannot be obtained by the competent and eager young physician who desires the best in gynecological training? We are in the position of the playwright who wrote an extraordinary play, requiring five elephants on the stage at once. The producer read the play and said, "This is fine but how do I get five elephants on the stage?" To which the playwright answered, "That is your problem, sir. I only write the plays." We have written the requirements for the prospective gynecologists but have failed to date to produce the residencies necessary to complete our obligation.

While still a young man in Philadelphia, Dr. Kelly began traveling abroad, and in 1886 he first visited England, Scotland, and Germany. While in Eng-

land he attended the meeting of the British Medical Association at Brighton. Lawson Tate gave the address in surgery. Kelly was invited to take part in the proceedings of the gynecological section and reported a case of unruptured tubal pregnancy diagnosed preoperatively and proved at operation. Tate remarked that he did not concur in the "cocksure diagnosis" of the young man and made light of his communication. Thus early in his career the future leader of American gynecology had an encounter with the then most dominant figure in abdominal surgery in England.

In 1888 he again visited Europe in company with Hunter Robb and Constantine Goodell. In Berlin he met Virchow, and worked on cadavers in an attempt to determine a method of ureteral catheterization. From Berlin the party went to Prague where they saw Pawlick catheterize the ureters blindly through the water-filled bladder. In 1889, he returned to Germany and married Laetitia Bredow in the Danzig Cathedral.

Kelly's early work on air cystoscopy and ureteral catheterization proved to be one of his greatest contributions to gynecology and led to the bitterest controversy in his medical career.

After visiting Pawlik's clinic in Prague in 1888, Kelly returned to Philadelphia, and began practicing catheterizing ureters blindly by fishing for the orifices in the water-filled bladder by Pawlik's method. He described this to the American profession as Pawlik's method in 1893. He began viewing the water-distended bladder through a cystoscope of his invention with the patient in the knee-chest posture in 1892. The instrument which was made for him had a glass partition to prevent the water from running out of the bladder. He inspected the bladder by direct vision, using a head mirror. One day a cystoscope was dropped by an assistant and the mirror was shattered. Shortly thereafter Kelly noticed that, with a patient in the knee-chest posture, air spontaneously rushed into the vagina. It occurred to him that the bladder might similarly be distended with air. To quote his resident of that year, John Clark, "The idea suddenly struck Dr. Kelly that the same effect would be produced on the bladder if air was allowed to enter it and he called for the short speculum from which the glass had fallen out and inserted it into the urethra. The bladder at once ballooned out and its walls could be inspected, and after some search the ureteral orifice on one side was located and the ureter catheterized under direct inspection for the first time."

In November, 1893, he published in the *Johns Hopkins Hospital Bulletin* "The Examination of the Female Bladder and the Catheterization of the Ureters under Direct Inspection." Other papers appeared in 1894 showing modifications of the cystoscope.

In 1896, there appeared in the *American Journal of Obstetrics* an article by Dr. W. Rubeska, an assistant of Dr. Pawlik, entitled, "A Criticism of Prof. Howard Kelly and His Discoveries in the Domain of Urinary Diseases." He stated that Kelly had observed a demonstration of ureteral catheterization in Pawlik's clinic in Prague and that Pawlik told him of his yet unpublished method of cystoscopy by distending the bladder with air with the patient in the knee-chest posture. He concluded by stating: "1. A Kelly ureteral catheter

does not exist. 2. That the so-called cystoscope of Kelly is entirely the discovery and intellectual property of Professor Pawlik."

Kelly had always had a keen interest in medical history, and in many of his scientific articles he prefaced the report of his contributions by a short chronological review of the discoveries up to that time, being careful to give credit where credit was due. He had no intention of letting Rubeska's claims go unchallenged. Fortunately, he had with him as a traveling companion in Prague Dr. W. C. Goodell who later wrote Kelly verifying the latter's statement that only the blind method of ureteral catheterization by "fishing" had been demonstrated to him and Dr. Kelly.

The training in cystoscopic methods and female urology was made a part of the training of Kelly's residents after that. To the author this is also a milestone in gynecological education. The symptoms resulting from disease of the urinary organs and the generative organs are frequently so closely intertwined that only by complete urological examination can the correct diagnosis be made. What could be more logical than to train gynecologists to make this examination in order to evaluate these symptoms? And yet how slowly has female urology been accepted as part of the training in gynecology in this country!

It was not long before Kelly's operating skill attracted many visitors to his amphitheater from this country and abroad. He was a real showman and a full gallery spurred him on in his fearless surgery. I recall one of his last visits to Hopkins for the purpose of operating for a visiting society. It was my residency year and I had the privilege of helping him. The occasion was the meeting of some surgical society and, for the convenience of the visitors, all the operations were done in Halsted's surgical amphitheater. The patient was on the table and draped for surgery when Dr. Kelly stepped into the operating room. As was his frequent custom in his later years he gave a brief historical review of the contemplated operation before stepping up to the table. The subject was a Negro woman with a huge fibroid. With one stroke of the knife he cut through the skin, fat, and fascia. The tumor was enormous and he began to push the dressings away and call for more room for a longer incision. He kept pushing the dressings and extending his incision to the upper abdomen. Fearing that his incision would soon extend beyond the sterilized area on the abdomen, I was worried. In the gynecological operating room where Kelly had worked for many years the operating table was so placed that the patient's head was at the north and the feet at the south end. In Halsted's amphitheater the reverse was true. Suddenly a thought came to my mind and I said, "Dr. Kelly, this is the head end of the patient." Without the slightest embarrassment he said, "My mistake," took the knife in his other hand (for he was quite ambidextrous), and extended the incision downward. The uterus was out in about ten minutes and the operating table pushed into a side operating room where the first assistant resident, Dr. George Gardner, closed the incision. A second patient was rolled in and I helped Dr. Kelly rapidly dispose of an ectopic pregnancy. After I had closed this incision I walked into the adjoining room to see how Gardner was getting along. I found him still sewing on the enormous incision of the first patient extending from symphysis to xiphoid.

Dr. Kelly's pioneering efforts in surgery were directed at techniques of hysterectomy, myomectomy, vesicovaginal fistula, rectovaginal fistula, ureteral and kidney surgery, and uterine suspensions, while Drs. Clark and Sampson, his residents, worked on the radical operation with lymph node dissection for cervical cancer. By temperament he was too impatient to be suited to obstetrics and in 1899 he put the department of obstetrics under the able direction of J. Whitridge Williams. Kelly was also not the man to spend hours at the microscope and he placed T. S. Cullen in charge of the pathological laboratory.

From the time of Dr. Kelly's graduation in 1882 he was a prolific writer. The subject of his first paper had to do with the assassination of President Garfield and was entitled, "Was the thoracic duct injured in the case of President Garfield?" Some issues of the *Johns Hopkins Hospital Bulletin* carried two or three articles by him. Up to 1919 he had been the author of 485 books and journal articles. While still in Philadelphia, he became a collector of early medical books and was enough of a bibliophile to interest Osler, with whom he often chatted about early editions after consultations. He took a leading part in the meetings of the Hopkins Medical History Club and was a charter member. Fifty years later at the golden anniversary of the Club he gave a lively review of the early years. He published about 60 articles on historical subjects. His writings were not always polished literature, as many were obviously hastily written, but on occasion he could and did write with a fine thoughtful style.

Kelly's contribution to medical illustrating was not the least of his accomplishments. Max Brödel had been brought to America by Professor Mall of the anatomy department. After a short time Brödel's services were taken over by Kelly who supported him until the University created the chair of Art as applied to Medicine as the result of a generous gift by Mr. Henry Walters. In fact, Kelly was turning out so much published work that two more artists, Becker and Horn, were brought from Germany to assist Brödel. Although Kelly's publications did much to establish these artists, they also helped establish Kelly's reputation in the eyes of the reading medical public. Kelly became so interested in medical illustrating that he wrote an article, "Art Applied to Medicine and Surgery," which was partly a historical review and partly propaganda for better illustrating.

From childhood Dr. Kelly had been interested in mineralogy. He spent several summers in Mexico, looking into the subject of mining. In 1903 he obtained a small amount of radium through Madame Curie. When it was discovered that there were deposits of radium in Colorado, Dr. Kelly and Dr. James Douglas of New York undertook to extract radium from the Colorado deposits. Secretary of the Interior Lane placed the best brains of the mining experts in his department at their disposal. Dr. Douglas gave his share of the radium thus obtained to the General Memorial Hospital of New York and Dr. Kelly's share came to Baltimore. He and his associate Dr. Burnam began treating malignancies, myomas, and functional bleeding with irradiation and contributed much to these now generally accepted therapeutic measures.

After thirty years as active head of the gynecological department of the Johns Hopkins University, Kelly resigned as Professor of Gynecology in 1919 at the age of 60. The circumstances leading to his resignation are recorded in the files of Edward H. Richardson in the form of a sheaf of personal letters from Howard Kelly to Sir William Osler, covering a period of 1911 to 1913. They were presented to Dr. Richardson in March, 1950, by Dr. W. W. Francis, nephew of Dr. Osler, who is Librarian and Literary Executor of the Osler Library at McGill University. They clearly indicate that Dr. Kelly thought injustices were perpetrated against him by the formulation of plans by certain faculty members for a transition to the full-time system at Hopkins. This report was circulated among the trusteees and served the purpose of making Kelly feel that his services were no longer acceptable as Professor of Gynecology. His own feelings were expressed in a letter to Sir William Osler written in May, 1911, from which the following is an excerpt: "Dear Osler: We confabulated last night from 8-11 o'c. All were for the change, putting the clinical men on salaries and cutting off all private work, except Myers and myself. Myers' objection to the change was that he was unwilling to yield his liberty, but he did not expect to do any practice. Finding I stood alone and my minority report was looked upon rather as an attempt at personal vindication than any criticism of the real matters at issue, I told them to go ahead and do whatever they conscientiously felt to be right without reference to me. I shall be very sorry but it will mean my retirement wholly into my private work. Williams will also be able to realize the great ambition of his life, the control of both gyn. and obst. This I think is a bad arrangement, but it may work well for a term of years, especially under his able management."

Some years elapsed before Kelly actually resigned but when he did in 1919 he was only 60, ten years before the stipulated retirement age, and at the height of his ability and career. Following the announcement a wave of indignation and resentment emanated from gynecologists whom he had trained and the Hopkins alumni in general, but Kelly's career as a teacher was over, broken on the rock of an ideology formulated by men who apparently believed the system which they envisioned was more important than the individual, no matter what the caliber of that individual might be.

Thus far we have concerned ourselves chiefly with Kelly's scientific accomplishments but his life was far broader than his profession. His interest in nature was derived from his mother who loved natural history. Kelly frequently spoke of these interests and believed that one's avocations had as much to do with the molding of one's character as his profession. Botany, mycology, astronomy, geology, and reptilia were among his avocations. Although his interest in these sciences was, according to his own statement, amateurish, he published several papers in these fields. He employed a full-time artist to draw and paint various fungi specimens. He assembled the best collection of books on mycology in this country, which he presented to the University of Michigan where he believed they could be best utilized. Snakes had always interested Dr. Kelly and in 1899 he wrote a paper on "The Recognition of the Poisonous Snakes of North America." In fact, he kept several of them

running freely about his house. On my last call upon Dr. Kelly about a year before his death, the door was opened by the butler and just behind him was an enormous snake coming down the hall steps. I found Dr. Kelly in his library and mentioned the snake to him. He recognized the snake from my description and was delighted, for he had not seen it for several weeks and feared that it had escaped from his house. Incidentally, when I entered the library he was amusing himself by permitting a tarantula which someone had brought him from one of the banana boats in Baltimore Harbor, to crawl over his hands. "See," he said, "it won't bite you if you don't annoy it."

At one memorable meeting of the Hopkins Medical Society he spoke on snakes. He had several with him to demonstrate his points. Everyone gasped when Dr. Kelly grasped a diamond-backed rattler by the nape of the neck with his left hand, held the tail in his right hand, and with it pointed out the snake's markings. There was a sigh of relief when he put the snake back into the gunny sack. But just at that moment the snake bit him through the burlap bag. For a moment he turned pale but continued on with his talk. The meeting was over in a few minutes and Dr. Kelly returned home, none the worse. The snake had been teased before being brought to the meeting and had discharged most, if not all of its venom.

Although an indefatigable worker, Kelly never neglected to take a long summer vacation at his camp north of Toronto on Lake Ahmic into which flows the beautiful Magnetawan River. There were the summer homes of many of his best friends: Abraham Flexner, Cullen, Brödel, and there is where real friendships were formed. He was an expert swimmer and canoeist. Fishing required a little more patience than he could afford, but he spent much of his time collecting botanical specimens in the woods. When well past middle life he broke his neck by striking the bottom of the lake while doing a high dive. On another occasion he almost lost his life on a daredevil canoe trip during high water on the Susquehanna River.

Dr. Kelly founded the first camp for underprivileged city boys in America at Ricketts Glen in Luzerne County, Pennsylvania, hoping to interest the youth in nature, from which he had received so much pleasure during his lifetime.

Dr. Kelly's mother was a deeply religious woman and he followed her example. His Bible was his constant companion. He had the Gospel of St. John printed in pamphlet form and distributed the booklets freely to anyone he chanced to meet—doctors, nurses, businessmen, and taxi drivers. In fact, he frequently tipped his taxi driver with one of these booklets. Although reared in the Episcopal church he recognized no denominational delineations. His activities suggest that he felt the Episcopalians were a bit too reserved and he often worked with the more evangelistic denominations. He spoke from some pulpit or in some Sunday school almost every Sunday. In fact he often worked so hard on Sunday that he was most difficult to assist in the operating room on Monday morning. This ministerial activity was not stopped in the summer, when he frequently preached in one of the country churches near his Canadian camp. He actively supported the evangelist, Billy Sunday,

while he held revival meetings in Baltimore, often sitting on the platform with him and urging his house staff to be present. In middle life he learned to play the organ for the purpose of playing gospel hymns.

One of his well-meant undertakings was directed at the red-light district in Baltimore and he spearheaded a spirited campaign to do away with it. According to Dr. Kelly's interpretation the district was eliminated; according to the more skeptical, the business was disseminated throughout the more respectable residential districts of Baltimore. But Kelly made a real attempt to rehabilitate these women to respectable society, even to the extent of inviting them to his own home. Dr. Samuel Crowe relates that while Dr. Kelly was entertaining a prominent British surgeon in his home on one occasion he placed the surgeon between two of these girls at the dinner table. In the course of the meal the conversation turned to the snakes that were crawling about the floor. Imagine the sentiments of the proper Britisher with snakes at his feet and a harlot at either elbow!

In his later years he usually wore a flower in his buttonhole and just below this a small button on which was a question mark. When asked, "What is the question?" he would reply, "What do you think of Jesus?" Imagine the dilemma in which this placed some of his friends!

In spite of Dr. Kelly's religious leanings he was reported to have charged some tremendous surgical fees as judged by today's standards. Just as the scientific compartment of his mind was airtight from his fundamentalist religion, so was the religious compartment airtight from the financial one. He gave of his services freely to the poor but the wealthy paid and paid well. His charities were many and very liberally given. Most of his donations were made to churches, missions, the education of missionaries' children, and for many years he underwrote the philanthropic work done by his sister, Mrs. Robert Bradford, at "The Lighthouse" in Philadelphia.

Probably the man best able to evaluate the life of Dr. Kelly was Dr. Welch. On the occasion of Kelly's seventy-fifth birthday Welch sent the following letter: "I have always felt, as did Osler, that you did more than any of us to extend the fame of the Johns Hopkins University to distant parts; and the hospital offered no greater attraction than the opportunity to see you and your work, and the new methods which you were so rapidly developing."

On Jan. 12, 1943, Dr. Kelly died of pneumonia at about 3:00 A.M. On the same morning at about 8 o'clock Mrs. Kelly followed him. A double funeral was held and they were laid to rest side by side on the brow of a hill, at a site picked by Dr. Kelly a few years before. It was close to the nature which he had loved. With the exception of the youngest son, Dr. Edmund Kelly, who was in the armed forces in the Pacific, all nine children were present at the funeral. Thus was terminated at the age of 85 the life of one of the most dynamic men of medical history, a man who did more to establish American gynecology as a surgical specialty than anyone before or since his generation. How true his prediction in 1912 had become: "Accordingly as we remember others so those yet to come will remember us."

HYPERTENSION DUE TO VASCULAR LESIONS OF ONE KIDNEY—ITS SIGNIFICANCE TO THE PROBLEM OF HYPERTENSION IN GENERAL*

JOHN EAGER HOWARD, M.D., BALTIMORE, MD.

(From Johns Hopkins University and Hospital)

I FEEL greatly flattered to be asked to speak to you today, but confess to some little trepidation before this audience. As an internist, whose medical off-hours have been spent in by-passes of endocrinology and metabolism, I sought a subject familiar to me which might prove of interest to the gynecologist. But surgeon and physician are both really medical physiologists, and hypertension is presently acclaimed as the commonest disease of civilized man. Furthermore, the definition of a hormone states it to be a substance made in one tissue which acts elsewhere at a distant site[1]; there is no specification as to whether the action must be for good or for evil. These remarks will concern hypertension as apparently induced by some substance or substances produced by the kidney under specific circumstances, namely, reduced arterial blood flow.

My interest in this subject came about in an unusual fashion; a young man got well because of a series of medical mistakes, both of the head and hand.[2]

Right lower quadrant pain led to appendectomy, but the appendix proved to be normal. A few days later the blood pressure was found to be elevated. Within three months full-blown malignant hypertension was present, with hemorrhagic and exudative retinitis but with good over-all kidney function. The presence of an epinephrine-secreting tumor was suspected, seemed unlikely on clinical grounds, but a mass was visualized on the perirenal air radiogram. Simultaneous exploration, as was then the custom, was made of the two sides; and the adrenal tumor proved to be mythical. During operation on the other side, however, the intern's fatigue allowed the retractor to slip, bringing into view the kidney which contained a sizable abnormal area of yellowish color. The kidney was removed in the belief that the mass was cancerous; section later showed it to be an infarct. After operation the patient's blood pressure began to fall, and within four months he was normotensive with no residual of his hypertensive retinopathy and with normal urine. His blood pressure is normal today, seventeen years later.

This unusual experience caused the speaker no undue inquisitiveness at the time but was stored in the cobwebs of memory for twelve years. There was then seen an almost exact replica of the first case.

A 45-year-old physician had fever and sore throat for which he treated himself with penicillin.[3] Six days later he developed sudden aching pain in the right lower quadrant, which would ease off and recur. Some hours later he noted rebound tenderness and sought

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surgical aid. A normal appendix was removed. During convalescence renal function and intravenous pyelography were normal, and no cause for his pain was disclosed. Three weeks later he returned to the hospital because mild right flank pain had been present since discharge, and he had found some albumin and occasional red blood cells in the urine. Mild hypertension was now noted, and a diagnosis of subacute hemorrhagic nephritis was made. Thereafter rapid progression of the hypertension occurred, and eight weeks after the original attack of pain the patient was readmitted. Advanced retinopathy was present so that he could not read, the blood pressure remained markedly elevated during Amytal and benzodioxane tests, renal function remained good, and intravenous pyelography revealed no abnormality of the calyceal system. The remarkable resemblance to the first case was explained to the patient, who readily agreed to exploration of the right kidney. The pyelograms were re-examined and, on comparison of recent films with those taken at the initial admission, the left seemed to have increased slightly in size, the right to have shrunk 1 cm. and 0.5 cm. in its diameters. The right kidney was removed; it contained a small infarct and a large area of parenchymal atrophy. The hypertension receded gradually, the patient returned to work in two months, and eight months later all evidence of the previous retinopathy had disappeared. Blood pressure was normal, and the patient has remained well during the past five years.

There seemed little doubt that in these two patients the removed kidney had been the offending agent in the production of the rapidly advancing hypertension, and that both had vascular insults to the kidney. Renal infarcts are a common finding at postmortem. Why did these patients and a few others reported develop hypertension, whereas the vast majority do not? Dr. Morgan Berthrong re-examined the kidneys of these patients together with many others which contained infarcts but which had *not* resulted in hypertension. It was found that in most renal infarcts the zone of necrotic tissue is sharply defined and abuts onto normal-appearing renal parenchyma. But in these two hypertensive patients there were surrounding zones of *atrophied* renal tubules, clear evidence of *reduced arterial supply* to still viable renal tissue. Further experiences to be related make it seem likely that most, if not all, instances in which *unilateral* renal disease causes hypertension are the result of reduced arterial flow to sizable areas of renal tissue, but that the flow is not reduced enough to cause death of the cells.[3b] This then is the analogue of the experimental hypertension first demonstrated by Janeway[4] forty-five years ago, with constricting ligatures about the renal arteries in dogs, and so clearly elaborated by Goldblatt's[5] classical studies.

Unilateral renal disease causing hypertension in man was first recognized in 1937 by Dr. Allan Butler,[6] whose patients recovered after removal of kidneys with unilateral pyelonephritis. Following this observation, there was a flurry of interest in the subject, and for a while many infected kidneys were removed in the hope that hypertension might thus be relieved. However, the percentage of successful results was so low as to be highly discouraging. Summarizing the situation in 1952, Perera[7] noted that in his rather large series the successful cases were those in which the hypertension had been of recent onset and was rapidly progressive. But a rapid clinical course, the history of a recent attack of unexplained abdominal pain, and radiographic evidence of atrophy seem flimsy evidence for nephrectomy, and further diagnostic criteria are needed. It is hoped that some progress has been made in

recognizing those patients whose hypertension is due to reduced blood flow to one kidney by the use of abdominal aortography, together with certain differential renal functional studies. It is believed also, from subsequent observations to be related, that further evidence has been provided that hypertension in man can be produced by reduced arterial flow to the kidney.

A 37-year-old man had right-sided abdominal pain interpreted as renal colic.[3b] There were microscopic hematuria and pyuria, but flat film and intravenous pyelography were normal. His blood pressure was then and had always been normal. Four months later he had headaches, and the blood pressure was found elevated. His physician noted rapid progression of the hypertension over the next two months, with appearance of retinal hemorrhages and exudates. Intravenous pyelography was interpreted as normal. The benzodioxane test was negative. Simultaneous catheterization of both ureters yielded *a lesser flow of urine from the right kidney and a lower concentration of sodium in this urine* than in that obtained from the other side. Arteriography disclosed a constriction of the right main renal artery. After right nephrectomy there was a rapid fall in blood pressure, the eye grounds cleared, and the patient has been normotensive and well for the subsequent eighteen months. The removed kidney *appeared entirely normal,* weighed 161 grams, and microscopically *no abnormalities of either the tubules or glomeruli could be seen.* Criticism has been leveled at this case on the ground that the narrowing in the renal artery as shown in the aortogram was an artifact or spasm produced by nearness of the needle. However, the man is well and it is hard for him, for us, or his physician to believe that the removed kidney was not causing his hypertension. It is our belief that here was arterial narrowing insufficient to result in visible tubular atrophy, yet sufficient to produce functional changes which resulted in hypertension.

A 4-year-old Negro boy was admitted to the hospital because of a convulsion.[3b, 8] His blood pressure previous to that time is not known. During the period of hospital study, it was usually around 200/140; at times readings were as high as 200/170. The urine could be concentrated to 1.028; the sediment was always normal; occasional traces of albumin were present. Retinal vessels were tortuous and constricted but papilledema, hemorrhages, and exudate were absent. *Intravenous pyelograms* and right retrograde pyelogram were normal. Unfortunately, the left ureter could not be catheterized owing to technical difficulties. The benzodioxane and Regitine tests were negative. In a retrograde arteriogram (catheter introduced via the femoral artery) no main renal artery could be demonstrated on the left side. However, the opaque medium did outline the left kidney and a tortuous left ureteral artery was visualized, suggesting retrograde flow through this vessel to the renal arterial tree. At operation a small tumor, later identified as a ganglioneuroma, was found lying in close approximation to the left renal pedicle. The tumor *and the kidney* were removed, for fear lest a still inadequate flow to the kidney might cause continuing hypertension, and a second operation might not be possible owing to the patient's precarious condition. The blood pressure fell gradually and on the fourteenth day was 140/70. Four months later the child felt entirely well, with a blood pressure of 128/72, which is slightly elevated for this age. The kidney specimen was perhaps barely smaller than normal. Microscopically there were small but definite foci of atrophy, and one small subcortical scar was thought to be a tiny healed infarct.

A 39-year-old merchant had been known to have had labile blood pressure for fourteen years (highest reading 155/105) but had been asymptomatic.[3b] On a vacation he suddenly developed headaches; exertional dyspnea and cardiac failure soon supervened. The blood pressure was found to be 240/130 at bed rest. Renal function was good, and there was no retinopathy. Intravenous pyelography revealed *no excretion of dye by the left kidney;* retrograde study showed no urine coming from the left ureter but the renal architecture was normal. The left kidney was removed. There were numerous adhesions of the perirenal fascia. There seemed to be reduced pulsation in the renal pedicle.

Microscopically the kidney showed *general atrophy* of the tubular epithelium. The blood pressure fell to normal by the seventh postoperative day, and the patient has felt well in the subsequent two years. He continues, however, to have mild hypertension *when under stress.*

It can hardly be doubted that, in the case histories just recited, the removed kidneys were the primary offenders in the production of the severe hypertension from which these patients suffered. The evidence that reduction in blood flow was the common denominator in the pathological function of the kidneys also seems very strong. Atrophy of tissue is a uniform response to relative ischemia, i.e., reduction of arterial blood flow of moderate degree but not severe enough to result in tissue death. In the case of the kidney, severely reduced flow results in atrophy of convoluted tubules while glomeruli remain intact for much longer periods. Berthrong believes this to be a consequence of the vascular needs of the highly complex metabolism of the tubular cell in contrast to that of the glomerulus which is a simple filtering structure.[3b]

In this group of cases we have one kidney which showed *generalized* uniform tubular atrophy. The main renal artery was not present, though in the hilum a number of small arteries entered the kidney. This kidney excreted no urine and no opaque medium was visible in the intravenous pyelogram. There was thus being carried on no normal renal function but something was being produced and secreted into the circulation which resulted in hypertension—analogous to Selye's[9] experimental "endocrine" kidney. In two other kidneys, those with infarcts, there were *zones of uniformly atrophied renal parenchyma,* indicating that vascular insufficiency had been present in these *still viable* areas. It will be recalled that intravenous pyelograms were read as normal in both these cases, though in retrospect it was noted that in one instance the kidney had shrunk slightly from its size in the film taken two months previously. In the remaining two cases, microscopic changes in the removed kidneys were minimal; in one of them the tubules appeared entirely normal even when stained by a variety of techniques. Intravenous pyelography was normal in these cases, too; yet in both instances defects in the renal arteries were demonstrated by aortography. We have postulated that there was not sufficient reduction in arterial flow to cause appreciable morphologic abnormality; yet functional changes were produced which resulted in hypertension. It is to be recalled that the kidneys of Goldblatt dogs with persistent hypertension only rarely show microscopic tissue changes.

Though the number of patients with hypertension who are amenable to relief from unilateral nephrectomy must be relatively small, their recognition is highly important, and knowledge derived from observations on them may shed light on the mechanism of hypertension in general. An attempt will now be made to emphasize certain features which appear to be useful as diagnostic clues and as possible indicators for nephrectomy.

In the first place it must be pointed out that the hypertension produced by unilateral renal disease presents the clinical picture of so-called essential hypertension, and cannot be distinguished from this disease at the bedside.

Perera's[7] observation was that, in his large series of nephrectomies, reduction in blood pressure followed operation most often in those patients whose hypertension was of recent origin and rapidly progressing, i.e., it resembled the so-called "malignant" type of essential hypertension. There appears to us, however, no particular reason why unilateral renal disease must inevitably result in this pattern, and pronounced improvement has been shown in some of our more recent cases after nephrectomy even when the hypertension has existed for as long as seven years.

A history of previously *unexplained* abdominal pain soon followed by hypertension should arouse suspicion of a renal vascular insult. It has become our custom to inquire whether after exploratory laparotomy the patient was told what was found, knowing the natural pleasure of our surgical confreres in being able to inform the subject that the appendix was red hot and about to burst.

If one is fortunate enough to have pyelograms taken previously to compare with new ones, one may be able to discern small shrinkage in one kidney and a slight compensatory hypertrophy in the other, as was demonstrated in two of our cases. But these changes were small, and one must be careful that the vertebral bodies are of identical width in the two sets of films before accepting the renal changes. If one finds no excretion of opaque medium on one side and the kidney smaller with no urinary excretion, the presumption is that this kidney is the offender. It will be recalled, however, that this set of circumstances occurred in only one of the five cases just reported; in the other four the intravenous pyelograms were read as normal. Voided urine specimens were likewise of little help, for the findings ranged from no abnormalities whatever to small quantities of albumin with or without red and white blood cells and casts. These observations certainly cast doubt upon such recent pronouncements on nephrectomy in hypertension by authorities as that "only seriously affected or non-functioning kidneys should be removed,"[10] and "the advisability of nephrectomy must rest upon conservative and recognized surgical indications, and not upon the hope of reducing blood pressure."[11]

In seeking a *renal functional* clue in patients with unilateral renal hypertension, White's[12] observations on the dog with varying degrees of constriction of one renal artery seemed to offer promise. Though White's animals did not develop hypertension (dogs usually do not with unilateral constriction), *small reductions of arterial flow resulted in a progressive fall in water and sodium excretion before there was any significant reduction in inulin or Diodrast clearance.* With progressively increasing constriction of the artery, of course, there did result reduction of all functions to the point of complete anuria. Findings exactly similar to those of White's *lesser* constrictions were observed in the third case outlined. On simultaneous catheterization of the ureters, 10 c.c. was obtained from the right, whereas 100 c.c. came from the left in half an hour. Sodium concentration was 11 meq. per liter in urine from the right, whereas it was 19 meq. from the left. It will be recalled that this man had good total phenolsulfonphthalein excretion, intravenous pyelograms were read as

normal, and there was only a trace of albumin in the urine. The aortogram disclosed the constriction of the right renal artery. Gross and microscopic changes in the removed kidney were minimal, but the blood pressure fell promptly and the patient remains well a year and a half later.

Two other more recent experiences with this procedure are also of interest.

A middle-aged man with progressive hypertension for four years had had unexplained abdominal pain three years before the hypertension was noted. Intravenous pyelograms were read as normal. Ureteral catheterizations yielded 9 c.c. from one side compared with 22 c.c. from the other, and the *lesser* urine contained 99 meq. of sodium per liter compared with 117 meq. per liter from the other side. These findings led to the performance of aortography which demonstrated a defect in the right renal vascular tree. Nephrectomy was performed and it was found that the kidney was supplied by a number of small anomalous arteries, no main vessel being present. There were multiple cholesterol emboli resulting in widespread tubular atrophy. The patient was greatly improved when seen two months after operation, and the blood pressure was but slightly elevated.

A child had three embolic phenomena following surgical ligation of a patent ductus; one resulted in hemiplegia, one occluding the right iliac was removed surgically, and the third caused right flank pain and was almost certainly an embolus to the kidney. Marked hypertension was noted approximately two weeks after the renal embolus. Intravenous pyelograms were normal. At ureteral catheterization leakage around the catheters unfortunately interfered with volume measurements, but sodium concentration of the urine from the right was 22 meq. per liter while that from the left was 31 meq.

In a small series of patients suffering with what we feel sure was essential hypertension, whom we consider therefore to be controls, no significant differences in the urine volume or sodium concentration from the two sides have so far been encountered. From these observations it seems justifiable to believe, tentatively at least, that White's[12] observations in the dog are also true of man, namely, that reduction in renal blood flow affects water excretion and sodium concentration recognizably, before changes in filtration rate or Diodrast clearance can be adequately detected. It is doubtful if at this writing the author would recommend nephrectomy in a hypertensive patient on findings of this sort alone, but in the absence of contraindications aortography would be advised. It is of some interest that recently we had the opportunity to observe three patients with chronic bilateral renal disease (two with pyelonephritis and one with glomerulonephritis), hypertension, and moderate renal insufficiency. In one of the pyelonephritis cases catheter specimens from the two ureters disclosed lesser volumes of urine from the kidney with poorer function but the concentration of sodium was *higher*. The inference was drawn hypothetically that the scarring in the smaller kidney had not reduced blood flow to *viable* renal tissue more on this side than it had on the other.

In proposing the procedure of bilateral ureteral catheterization studies on persons suspected of having unilateral renal hypertension, certain precautionary suggestions need be made. We believed at first, from certain statements in the older literature, that the mere mechanical introduction of the catheters might reflexly affect renal mechanisms and obviate the findings. So far in our limited experience with the proved cases and the "controls" with essential hypertension, this has not occurred. The danger of introducing a urinary tract in

fection should also not be ignored, but if proper selection of cases is made and antibiotics are used coincidently, this risk seems warranted by the possible information to be gained. Leakage around one or both catheters may be detected by the finding of bladder urine at the end of the procedure, in which case only the sodium concentrations can be compared. Since most patients with hypertension are nowadays given very low sodium diets, often resulting in low serum sodium concentration, we have recently permitted normal diets for several days prior to the examination in order that adequate sodium excretion may occur for better recognizable differences between the two sides. We do not know at this time *how much* difference in water and sodium excretion between the two sides is significant; thus far the patients with proved unilateral renal vascular disease have shown more than 50 per cent difference in the excretion of water and at least 15 per cent reduction in sodium concentration. The total sodium output by the affected kidneys has, therefore, been markedly reduced in every instance.

Aortography has been of great value and highly definitive in all the proved cases in which it has been carried out. The technique is not simple and the procedure should be carried out only by experienced hands. In patients who have had sympathectomies shortly after arteriography, periaortal hematomas have sometimes been found. The dose of opaque medium must necessarily be large and every precaution should be taken that the aorta is the injection site and that some smaller vessel does not receive so large a load with necrotizing results to the tissues supplied by it.

A few words before closing on the possible inferences to be drawn from unilateral renal hypertension as to the mechanism of hypertension in general. Pathologic studies on patients who have had prolonged sustained hypertension, without primary renal disease or adrenal medullary tumors, have almost invariably disclosed morphologic changes in the renal vascular bed compatible with vascular insufficiency of these organs. Furthermore at autopsy kidneys are not seen with *generalized* arteriolar narrowing of marked degree from persons who have not had hypertension. In experimental hypertension produced by unilateral renal artery constriction, arteriolosclerosis is found in the opposite or "good" kidney. The evidence appears heavily weighted in favor of the theses that reduced arterial flow can produce in the kidney some functional change that results in hypertension, and that *hypertension results* in anatomical changes which reduce renal blood flow. Most pathologists would agree, I believe, that once arteriolosclerosis has been produced in a vessel there is little likelihood of reversal. But if only a few vessels, patchily dispersed, have been affected at the time when the primary cause of hypertension is removed, it seems possible that great falls in blood pressure might ensue. In Thompson and Smithwick's[10] cases of unilateral renal hypertension relieved by nephrectomy, biopsy of the other kidney revealed arteriolar changes, in one instance advanced. The biopsies were naturally taken only from the cortex, however, and only a very limited sample of the kidney was represented.

It will be recalled that we did not use the term "cure" for the result in any of our patients who had nephrectomies. Indeed, most of them still manifest some tendency to hypertension. They are individuals with so-called labile blood pressures, who under normal resting conditions are normotensive or nearly so, but under stresses manifest abnormal rises. Their reactions in this regard are analagous to those of persons with early "essential" hypertension. Whether their inherent vasomotor makeup made them liable to this situation and indeed permitted the unilateral renal disease to produce the drastic hypertension that it did, or whether the hypertension suffered from their offending kidneys left them with some reduction in over-all renal arterial flow to the remaining kidney is purely speculative.

It is interesting, however, to note the analogous features of their behavior to those other rare instances of hypertension which are amenable to medical or surgical attack. A considerable proportion of patients with adrenal medullary tumors have *persistent* hypertension, indistinguishable on purely clinical grounds from "essential" hypertension. Some of these individuals go into shock promptly when the tumor is severed from the general circulation, as though its secretions alone had been maintaining the blood pressure. Others, however, with equally successful end results show no waver in their hypertension at the time of the tumor's removal, but show a gradual fall to normotension over succeeding weeks.[13] Patients with hypertension of Cushing's syndrome, when an adrenal tumor or hyperplastic adrenals are removed, aside from the immediate period of operative shock, show *gradual* fall thereafter to normotensive levels. These removals of offending agents are followed by blood pressure behavior strikingly parallel to that seen after excision of a kidney with reduced arterial flow. Likewise, when coarctation of the aorta is surgically alleviated, there is seldom seen a precipitous fall in the blood pressure of the upper portion of the body; rather there is a slow fall requiring two to three weeks before normotensive levels are reached.[14] One cannot help wondering if the mechanism of hypertension in these conditions may not be reduced renal vascular flow.

The same may be hypothecated in regard to essential hypertension. Successful thoracolumbar sympathectomy is followed by a *gradual* fall in blood pressure, at least in the recumbent posture, and success or failure of these operations cannot be correlated directly with results of the interruption of the nerves to the limbs as judged by skin resistance tests.[15] Some patients with dry warm feet and very high skin resistance, indicative of perfect surgical interference of sympathetic innervation, nevertheless manifest no improvement in their hypertension, and vice versa. It may be that sympathectomies when successful have increased the renal arterial flow; when unsuccessful they have not. Currently studies are projected in an effort to see whether patients with essential hypertension can, under temporary dilating stimuli, be shown to excrete more sodium and water than they excrete under normal conditions. Such patients might be favorably affected by sympathectomy, those not so responding being unfavorable candidates for the procedure. So far no criteria have evolved to our knowledge which will allow accurate prediction of the

success or failure of this operation, which is admittedly of great benefit in a limited percentage of cases.

To believe that in most types of hypertension in man a renal mechanism is involved offers a more optimistic outlook that better therapeutic approaches may be devised against this common disorder. Reduction of arterial blood flow to viable renal tissue seems the most likely cause of the renal production of a hypertensive agent. Recent experimental observations by Wakerlin's[16] group suggest a similar mechanism for "essential" hypertension and "renal" hypertension. Renin is a material, derivable from normal kidney cortex, which, when injected into normal animals, acts upon a globulin in the blood plasma to form a hypertensive agent. Being a protein, renin derived from one species acts as a foreign protein when injected into another species, and an antibody to the original renin is formed. Antibody formed to hog renin will neutralize dog renin and will prevent and overcome experimental renal hypertension in dogs. Hog renin therapy has also been shown to be successful against the so-called "spontaneous" hypertension in the dog, which closely resembles essential hypertension in man. Unfortunately experiments thus far seem to indicate that when hog renin is given to man, though an antibody is produced, this antibody is not effective against human renin.[16] Nevertheless, further pursuit of studies on these mechanisms is eagerly awaited.

The speculative remarks, made latterly in regard to hypertension in general, have been meant only to emphasize the author's view that the Goldblatt phenomenon does occur in man and perhaps far more generally than in the few cases of unilateral renal disease. But these matters are pertinent also to the identification of the unilateral renal cases, i.e., when to remove a kidney with expectation of benefit to the hypertension and when not to. In *all* the successful cases of nephrectomy in the literature to our knowledge and in all our own cases, there has been no great reduction in *total* renal function when the patients were tested in good states of hydration and with normal serum electrolyte concentrations. At the moment we would not recommend the operation unless such reasonably good function could be demonstrated in the kidney which was to remain.

Summary

In summarizing these remarks one might say that further evidence has been provided that hypertension in man can be produced by reduction of arterial flow to one kidney. Though probably rare among the vast number of hypertensive patients, such patients will be greatly benefited by nephrectomy. Certain suggestions have been made from which it is hoped that cases of this kind may be better recognized.

If there has been any merit in these remarks, I should be less than honest if confession were not made of the invaluable aid given by many of my medical colleagues, radiologists, and urological confreres. Their knowledge and ideas have been freely drawn upon, most especially those of Dr. Morgan Berthrong in the sphere of pathology.

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PROBABLE MESONEPHRIC ORIGIN OF CERTAIN FEMALE GENITAL TUMORS*

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AT THE very outset of this paper, we feel that we should make plain that our use of the term "mesonephric" in referring to the histogenesis of certain genital as well as certain renal tumors is not to be taken too literally, because of the lack of knowledge as to the embryologic and histologic transition between the mesonephros and the metanephros, or definitive kidney. These gaps in our knowledge are evident in the textbooks of embryology which we have consulted, and are freely conceded by the embryologists with whom we have discussed the question, notably Dr. George W. Corner, the director of the Carnegie Institute of Embryology, and his associate, Dr. George W. Bartelmez. They have permitted us to quote a written communication from them which, it seems to us, crystallizes some of these still unknown embryologic questions, some of which have a very direct bearing on the chief thesis of our paper.

"The urinary excretory system of vertebrates is formed from a continuous series of units, which reach a progressively higher order of differentiation from the cranial to the caudal end of the series. In mammals the metanephros or definitive kidney is topographically distinct from the mesonephros and its units are histologically and cytologically somewhat different from those of the mesonephros (for example, the brush border of the proximal convoluted tubule does not appear in the mesonephros). The two nephric organs are, however, derived from the same embryonic tissues, i.e., the mesonephric duct and intermediate mesoderm. The mesoderm which gives rise to the secretory tubules of the permanent kidney is merely situated at a more caudal level than that which forms mesonephric tubules. . . .

"It might be confusing to say simply that the kidney is mesonephric, in discussing the origin of tumors; it would be safer to say that the permanent kidney is developed from the same elementary tissues as the mesonephros. From the embryological standpoint it appears that each of the serial urinary organs (pronephros, mesonephros, and metanephros) might be expected to form tumor cells of similar character. It is difficult, for example, to distinguish the cells of the mesonephric tubules from those of the distal convoluted tubules of the permanent kidney."

The views expressed by Drs. Corner and Bartelmez are exactly the ones which we had arrived at after a review of the literature. We hope, therefore, that those who read this paper will not hold us to a strict accounting in our

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use of the term mesonephric, and will appreciate that in a good many instances a more nearly correct one would probably have been meso-metanephric. As a matter of fact, we shall take the liberty at times of using the latter noncommittal designation.

Historical Considerations

It was Meyer who, more than a half century ago, emphasized the mesonephric origin of at least some of the lesions which we propose to discuss today. The early embryology of the female genital organs cannot be discussed without consideration of the fundamental and dual role played by the mesonephros in the development of the female genitourinary apparatus. The story is a long and intricate one, which we shall sketch only briefly, merely summarizing the embryologic contributions of others, and trying to show their applicability to the pathologic studies comprised in the present paper.

The early work of Meyer was not the first in this field, but it was the most complete and provocative. It dealt chiefly with the role of mesonephric elements in the cervix and vaginal fornix in the production of certain rare pathologic entities in these locations. Only a very few American papers dealing with this subject have ever been published, notably those of Wolfe (1940), Huffman (1948) and Gardner, Greene, and Peckham (1948). The first two of these papers dealt with lesions of the cervix which may arise from cervical mesonephric vestiges, although the much earlier publications of Meyer had demonstrated a similar histogenesis for certain rare lesions of the vaginal fornix. The paper of Huffman especially is extremely complete and informative, including a more satisfactory review of the embryologic history of the mesonephros than is available in most textbooks of embryology.

The third of the previously mentioned trio of papers, that of Gardner, Greene, and Peckham, represented an exhaustive study of the histogenesis of the various types of cyst which may be found in the broad ligament, including a description of the criteria for the differentiation of mesonephric and paramesonephric cysts. In this paper, the authors make a strong plea for a revision of the nomenclature through the abandoment of eponymic designations, as so many have done in past years. They thus urge the discontinuance of such eponymic terms as Wolffian, Müllerian, and Fallopian and the substitution of such scientific designations for the indicated structures as mesonephric, paramesonephric, and oviduct. It would be difficult for anyone to argue against the rationale of such a reform, but some of us will be rather pessimistic about the practicability of its accomplishment in view of the long and deep entrenchment of some of these eponyms. This difficulty will be illustrated by a few of our own lapses in this paper, although we have tried to make at least some contribution to the crusade of reform.

The total reported number of lesions derived from mesonephric elements is so small that it is not strange that most reports have been of single cases or of very small groups pertaining usually to some one or two locations. The fact that the mesonephric and paramesonephric structures are present in both sexes, and that in the early weeks of development their relationship is intimate

and at times overlapping, makes it easy to understand why vestiges of the mesonephric body or ducts may persist and why they may be abnormally segregated in the purely genital areas derived from the paramesonephric ducts. In some cases such persistent or abnormally placed mesonephric elements may actually be demonstrated, and even at times their continuity with the lesions to which they may give rise. There are other lesions in which such a mesonephric origin cannot be so clearly established, but in which it is highly probable because of their location or, even more, because they exhibit certain microscopic characteristics which seem to occur as a sort of common denominator in lesions of mesonephric origin. A good many of our cases are of this type.

The fact that certain cystic lesions of mesonephric origin can occur in the broad ligaments or in the vagina has long been known. Reference has already been made to the excellent study by Gardner, Greene, and Peckham on the histogenesis and histology of broad-ligament cysts, and we shall make mention of one or two cases of solid tumors of the broad ligaments because of their apparent bearing on our general thesis. We shall not include in our paper any discussion of the fairly common vaginal cysts of mesonephric or Gartner-duct origin, again limiting ourselves to the solid tumors arising from the mesonephric-duct elements, especially those often occurring in the lateral fornices of the vagina. It will thus be seen that our group of cases is very selective, including chiefly those of ovarian, cervical, and vaginal nature, simply because it is in these locations that one encounters the rare instances in which the mesonephric elements appear at times to be the histogenetic source of neoplastic lesions.

Embryologic Considerations

It will be recalled that the mesonephric duct appears very early in embryonic life, at about a 4 mm. stage, and results from the fusion of a few of the pronephric tubules. The pronephric duct, like the pronephric tubules, never assumes any functional role, but it actually becomes the mesonephric duct, which rapidly develops its system of mesonephric tubules, numbering, according to Patten, something like 30 to 34 on each side in embryos of from 4 to 9 weeks. Caudally the mesonephric ducts empty into the cloaca, and later into the urogenital sinus. The paramesonephric ducts develop considerably later than the mesonephric, coursing along the median side of the latter for a distance and then crossing to its outer side. The later fusion of the paramesonephric ducts to form the uterus and vagina is well known, the cephalic unfused portions becoming the tubes.

The mesonephric ducts, so important in the formation of the male genitourinary apparatus, regress in the female, but fragments of the ducts may persist as vestiges in certain segments of the female genital canal, as already mentioned. Robert Meyer deserves the chief credit in the study of these occasional vestiges and in recognizing that they may be the origin of certain pathologic lesions.

In the female the remnants of the mesonephric ducts, as well as a certain number of the tubules, persist in the mesosalpinx in close relation to the hilum of the ovary, where they form the epoöphoron or parovarium. The main duct of the latter is the mesonephric duct proper, which then courses through the broad ligament close to the uterus, but practically never through the uterine structure until about the level of the internal os, when it penetrates into the substance of the cervix. A rather marked ampullary widening of the duct can be demonstrated in fetuses of even a very early stage, with later the development of bilateral ramifications and invaginations almost encircling the cervix and, what is of interest to our present discussion, extending into the lateral fornices of the vagina. Beyond this the vestiges of the mesonephric duct constitute the so-called Gartner duct which may give rise to the not so rare Gartner-duct cysts of the vagina.

What has been said constitutes only a very brief and elementary sketch of the embryonic status of the mesonephric duct in the female, and especially the possibility of persistence of fragmentary vestiges. As a matter of fact, Meyer found that fully 20 per cent of the fetal uteri he so meticulously studied showed cervical vestiges of the mesonephric duct, reaching full development at about the seventh or eighth fetal month. From our present standpoint, it is important to know that such vestiges may occur in the adult cervix and vaginal vault, as well as in the form of the Gartner-duct vestiges in the anterolateral wall of the vaginal canal.

How often such cervical mesonephric vestiges can actually be found would obviously depend upon the thoroughness with which they are searched for, and serial studies such as those made by Meyer upon a large number of fetuses at various ages would of course give a far higher incidence of such remnants than the estimates based on the examination of the one to a few sections ordinarily made for routine laboratory examination. Other than the high incidence mentioned by Meyer the only other figures we have seen are those of Wolfe and Huffman, both made on routine laboratory study of cervices. The former found cervical mesonephric vestiges in only 1 of 1,413 cervices, while Huffman reports finding nonneoplastic mesonephric ducts in 5 of 1,192 specimens. The rather large group of cases reported in our paper represents a selected group and of course would not be an index of the general incidence of such findings. Our own estimate of the incidence of such findings would certainly not exceed the 1 per cent estimate of Huffman. Incidentally, there is at least one case in the literature, that of Sakuraoka, quoted by Wolfe,[3] in which the entire mesonephric duct is said to have persisted, but the rule is for the vestiges, when they do occur, to be only patchy and fragmentary.

To recapitulate, mesonephric elements may occur in intimate contact with but not actually in the ovary, in the broad ligament, the cervix, and the vagina. In rare instances they may occur in the corpus uteri, but we have encountered no instance of this. It is therefore not surprising that the lesions we are reporting today as being of probable mesonephric origin consist chiefly of certain tumors of the ovary, broad ligament, cervix, and vagina. We may

again add that we are not including in our study the simple cysts of the broad ligament and vagina which are at least relatively common but which are of the type of simple retention cysts rather than neoplasms. As a matter of fact, we shall make no pretense of relating the constituents of the various tumors which we are reporting to the ducts or tubules, since we do not think that this is always possible with neoplastic growths, which often show marked dedifferentiation and atypia.

To emphasize still more the rarity of the group of lesions which we are presenting, only a small fraction of these have been encountered in the large material of our own department, the others having been sent to us for examination by gynecologists and pathologists in various parts of the country. Our thanks to those who have permitted us to include their cases in this paper are duly acknowledged in the reports of these cases. Unfortunately, as is so often the case, the clinical data accompanying the sections was almost always meager, and later efforts to amplify it or to ascertain the later course of the patients have often met with very little reward. This inadequacy of clinical information, however, has not seemed to us a serious handicap in the presentation of our chief thesis, which is the strictly pathologic one of trying to establish the probable mesonephric origin of certain rare pelvic tumors.

Possible Role of Mesonephric Elements in Certain Tumors of Ovary

There are two tumors of the ovary in which we believe an origin from mesonephric structures is highly probable, and between which we believe a much closer relationship exists than has apparently been suspected. The first of these is the tumor form described by Schiller in 1939, and designated by him as mesonephroma because of the origin from mesonephric structures which Schiller ascribed to it. His grounds for this were as follows: (1) the tumor cells resemble the endothelium of the glomeruli; (2) the tumors show isolated structural units which Schiller believes resemble the mesonephric glomerulus-like structures; (3) the structure of the tumors is characteristically tubular, the tubules resembling those of the mesonephros; (4) the tumors may occur at the site normally occupied by the mesonephros, i.e., the broad ligament close to the ovary. In one of Schiller's cases, this was actually the site of such a tumor.

As to the distinctive histologic picture presented by the so-called Schiller mesonephroma there can be no doubt, but a number of authors have taken issue with Schiller as to the mesonephric derivation of such tumors. This has been done most sharply by Kazancigil, Laqueur, and Ladewig, but others who have not accepted the mesonephric derivation of these tumors have been Jones and Seegar and also Stromme and Traut. The latter looked upon this variety of tumor as representing a teratoid adenocystoma of the ovary, and we ourselves wondered if this particular tumor pattern might represent only a variant of papillary serous adenocarcinoma of the ovary. It would take us too far afield to discuss all the pros and cons of this question, and the chief reason for drawing this type of mesonephroma into our present discussion is

that we believe our study has furnished a new type of evidence to indicate that the Schiller type of mesonephroma is actually of mesonephric origin.

It seems to us that both Schiller and those whose views differ from his put too much stress upon the significance of the glomerular structures sometimes found in the so-called mesonephromas. Emphasis on this point would suggest that the entire kidney structure is mesonephric in origin, and this is certainly not the case. The prevailing viewpoint at present is that the ureter and kidney pelvis are derived from the metanephric diverticulum, an out growth from the mesonephric duct, but that the real parenchyma of the metanephros or permanent kidney, including all the secretary tubules, is derived from the mesoderm of the nephrogenic cord which the mesonephric diverticulum collects about its distal end, according to the description given by Patten.

There is considerable confusion on this point among writers of textbooks, and we mention this because Schiller has stressed the resemblance of the papillary tufts in his mesonephromas to the glomeruli of the kidney. In spite of this we think that there is good reason to believe that these tumors are actually of mesonephric or, perhaps better, mesometanephric origin.

The chief reasons for our interest in the Schiller type of mesonephroma in our present study are (1) that certain lesions of the cervix and vagina, in sites where no other than a mesonephric origin seems tenable, and where a direct transition to mesonephric vestiges can at times be demonstrated, are indistinguishable histologically from the ovarian type of Schiller mesonephroma, and (2) because the latter type of lesion may, as we shall show, exist side by side, at times incorporated in the same neoplasm, with the now well-known clear-cell carcinoma of the ovary. In 1944 Saphir and Lackner called attention to the exact histologic similarity of these tumors with the clear-cell adenocarcinomas of the kidney, the group formerly so universally misinterpreted as hypernephromas. These authors, largely because of this fact, postulated a mesonephric origin of the clear-cell carcinomas of the kidney, and we know of no publication which has taken issue with this concept. Yet this obviously takes no cognizance of the combined roles of the mesonephros and metanephros in the formation of the definitive kidney, as has already been discussed. We question whether anyone can point definitely to any one cell type in either the meso- or metanephros which is unequivocally the source of the large, clear, glassy epithelial cells which are so characteristic of the clear-cell kidney adenocarcinomas, characteristics which rather naturally led to their former identification with adrenal cortical epithelium. At times one finds a rather low cuboidal or columnar clear epithelium in the mesonephric tubules, but not especially resembling the large glassy cells, often occurring in considerable sheets, which led to the original designation of hypernephroma of the kidney.

We have had the opportunity of studying a considerable group of mesonephromas of the Schiller type, and at least a moderate group of the somewhat less common clear-cell carcinomas of the ovary, including a considerable number of both from the Ovarian Tumor Registry. It should be mentioned that with few exceptions the pathologic material available for study of cases con-

tributed to the Registry consists of a few more or less representative slides. Even this very restricted study has revealed a good many instances in which the two tumor patterns under discussion are combined in one and the same tumor, and often, for that matter, in one microscopic field. Frequent as this observation has been, there is not the slightest doubt in our minds that the coexistence of these patterns would be far more common if it had been possible to have for study many sections from various parts of the tumors. Figs. 1 and 2 and others of the same group which might be adduced show not only the two coexisting types, but all shades of intervening transition from the Schiller mesonephroma with very low, short-peg-like or hobnail epithelium, to areas of similar tubular pattern but with a lining of large, clear epithelial cells, to definite adenocarcinomas in which many of the lumina are filled with large fields of the characteristic large, clear cells which so definitely resemble adrenal cells that it is not surprising that the exactly similar tumors which occur in the kidney were formerly called hypernephromas. As already mentioned, the mesonephric origin of these kidney tumors is now rather generally accepted, and a similar derivation inevitably suggests itself for the clear-cell ovarian carcinomas. How can one doubt a similar histogenesis for the Schiller type of mesonephroma which so often is coexistent, especially in view of the demonstrable transition of one pattern to another?

We have said nothing as to the papillary, glomerulus-like tufts which were formerly so strongly stressed as occurring in the Schiller mesonephroma, and which have been the cause of much difference of opinion. As a matter of fact, the chief basis for the rejection of a mesonephric origin on the part of Kazancigil, Laqueur, and Ladewig was that their studies did not confirm the actually glomerular nature of these papillary tufts. To us such an objection appears irrelevant, and for that matter it is not surprising that the tufts are only infrequently observed. It would be no more essential to expect to find such well-differentiated elements as glomeruli in all tumors of mesonephric origin than to expect well-differentiated seminiferous tubules or Leydig cells in all arrhenoblastomas.

The same type of evidence is available for the probable mesonephric origin of the Schiller mesonephroma and the clear-cell carcinoma when they coexist elsewhere, as in the vaginal fornix, as will be discussed later (Case 4).

Broad Ligament

In spite of the relative frequency of simple mesonephric cysts, usually very tiny and clinically unimportant, in the broad ligament, only a very few instances have been reported of genuine neoplasms of the broad ligament in which a mesonephric origin can properly be suspected. In a very recent paper, Lennox and Meagher report a case of parovarian carcinoma, and state that they have been unable to find any previous report of such a lesion. Their search of the literature, however, revealed 2 cases of benign papillary parovarian cyst, those of Nicholson in 1923, and Müller in 1942. We were particularly interested in the case of parovarian tumor reported by Nicholson in

1923, because of the similarity of the histologic pattern of his tumor with a broad-ligament tumor in our own group. In Nicholson's case the tumor was a papillary one growing into a cyst of the parovarium, which is quite generally accepted as of mesonephric origin. Our own case is as follows:

CASE 1.—Gyn. Path. 35007. For the material of this case we are indebted to Dr. O. S. Lloyd of Baltimore, who in 1926 performed the operation for the removal of the tumor. The patient was a white woman of 25, with a large papillary tumor arising from the posterior face of the right broad ligament close to the right ovary, though both ovaries themselves were completely uninvolved. As the tumor was thought at operation to be malignant a subtotal hysterectomy and bilateral salpingo-oophorectomy were done.

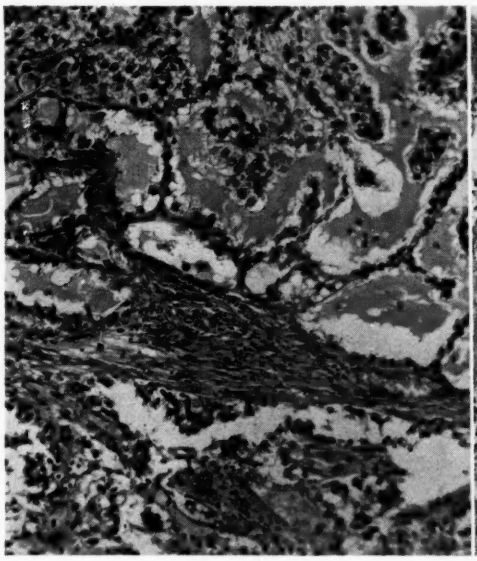

Fig. 1.

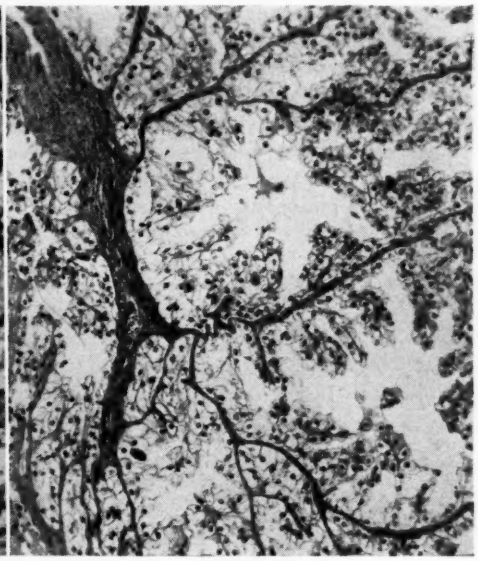

Fig. 2.

Fig. 1.—Gyn. Path. 93956. Mesonephroma of ovary showing also areas of the large clear cells (right) characterizing the clear-cell or hypernephroid tumors now considered mesonephric, though they were formerly called hypernephromas. For a high power of the characteristic large, clear cells see Fig 2. Kindness of Dr. Lyman Stowe, San Francisco.

Fig. 2.—Gyn. Path. 93956. Typical large, glassy cells in another field of same ovarian mesonephroma shown in preceding picture.

The microscopic examination, however, showed a picture which at the time was unique in our experience. The definitely papillary growth showed a peculiar finely tubular structure, mingling with narrow cords, and with a light textured connective-tissue stroma. There was no evidence of anaplastic activity, and we thought the tumor to be benign. This view has been borne out, because the patient is still living after twenty-eight years. Since we thought that the tumor was of mesonephric origin, we at that time coined the term "papillary mesonephroma" for indexing purposes, many years before the designation of mesonephroma was applied by Schiller to an ovarian tumor of different microscopic appearance, though supposedly also of mesonephric derivation.

Another and totally different solid broad-ligament tumor which at least suggests to us a mesonephric origin is the following:

CASE 2.—OTR 1112. This case is included in this series with some hesitancy and in a more or less tentative fashion, because it presents a structure different from that of any other tumor of supposedly mesonephric derivation which we have observed or which, so

far as we know, has been reported in the literature. For permission to make brief mention of this case we are greatly indebted to Dr. Joseph A. Hardy, Professor of Obstetrics and Gynecology at St. Louis University School of Medicine, and Dr. Hollis Allen, pathologist at St. John's Hospital, St. Louis.

The patient was a white widow of 63, with no especial symptoms except for dragging pain and a mass in the lower abdomen. There was no vaginal bleeding. At operation on Sept. 20, 1952, a myomatous uterus was revealed, but in addition the right adnexa were found distorted by the presence of a large mass, weighing 1,525 grams, located between the folds of the broad ligament and separate from the uterus. The right tube was stretched over the surface of the tumor, which was apparently closely attached to the right ovary, though the latter was small and atrophic. In other words, the tumor was obviously located in the mesosalpinx.

Microscopic study showed the matrix of the tumor to be dominantly a rather edematous fibrous tissue, but the particular feature was the discrete scattering of fine tubules lined by a very low epithelium and resembling closely the tubules seen in the preceding case of papillary broad-ligament tumor (Gyn. Path. 35007), which incidentally arose from an exactly similar location, in the mesosalpinx, closely attached to but separate from the ovary, just where one might expect a mesonephric tumor to arise. We do not know any other plausible explanation for the tubules of this tumor than that they are derivatives of mesonephric elements, though we know no case report of a similarly solid tumor to which such a histogenesis has been ascribed.

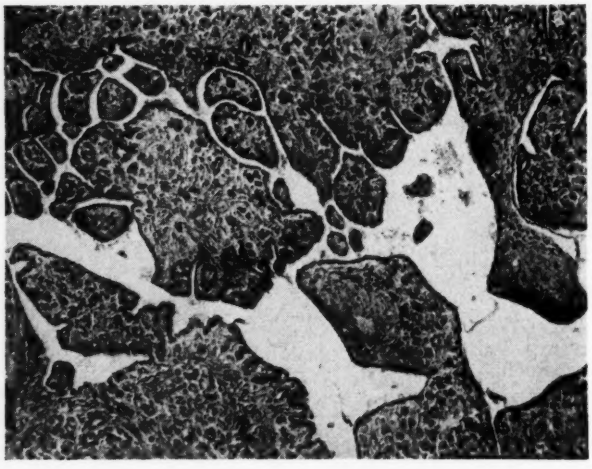

Fig. 3.—Case 1. Gyn. Path. 35007. Section of large papillary tumor arising from posterior surface of broad ligament close to but not involving ovary. Patient well after twenty-eight years. Tumor interpreted as benign papillary mesonephroma. Case of Dr. O. S. Lloyd.

Cervical and Vaginal Mesonephric Lesions

Huffman in 1948 performed a real service not only in his exhaustive review of the very scant literature of the subject, but also in collecting all of the published reports of lesions of the cervix in which a mesonephric origin had been established. He was able to find only 2 reports of cervical cysts of mesonephric-duct origin, those of Dworzak and Henkel. However, Meyer mentions having observed, in addition to adenomatous hyperplasia of the mesonephric-duct remnants in the cervix, instances of intracystic papillary growths, and pictures such a lesion in his article in Vol. VII of the Henke-

Lubarsch *Handbuch* (Fig. 351, page 532), in which simple tubules were transformed into solid columns with disappearance of the original tubular structure, as a matter of fact, becoming malignant. This particular papillomatous area in Meyer's case is similar to the papillomatous tumor of the broad ligament shown in our Fig. 3, which in spite of its rather large size was clinically benign. There can be very little doubt as to the mesonephric origin of both these lesions.

Meyer's allusion to a number of other lesions of what he was inclined to interpret as Wolffian duct origin seems to us to be rather doubtful, since he speaks of the association of muscular overgrowth, and since Meyer's original acceptance of von Recklinghausen's concept of the Wolffian duct origin of adenomyoma of the uterus makes it likely that the cases he mentions were really instances of adenomyomas.

In discussing the histogenesis of mesonephric neoplasms of the cervix and vagina, one might almost group them together because a good many of these tumors involve both these locations, and it is not always easy to be sure which is the primary seat. In this respect one finds the same confusion with a totally different tumor, sarcoma botryoides, which is sometimes reported as arising in the cervix, sometimes in the vaginal vault, and often involves both.

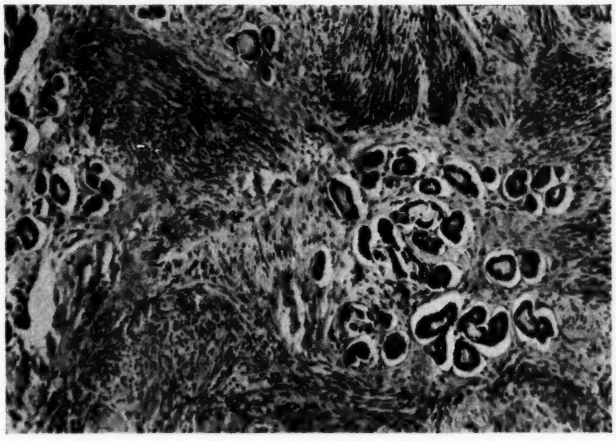

Fig. 4.—Gyn. Path. 95031. Adenoma-like cluster of mesonephric tubules in cervix. Carcinoma may in rare cases arise from such rests. See 3 instances following.

Only in extremely rare cases does the uterine body show any mesonephric remnants, since the duct only exceptionally penetrates the uterus above the internal os. As has already been said, it is in the cervix and vaginal vault that one is likely to find lesions of mesonephric origin, though their rarity has already been emphasized, as well as the rarity of even simple nonneoplastic vestiges. Some of the simple lesions derived from these remnants are small and unimpressive, such as the tiny cysts or cystadenomas, and it is sometimes difficult to draw the line between the normal and the abnormal. The adenomas are characterized by considerable clusters of the small coiled canals or tubules, often resembling small gland lumina. In some of the reported cases, like that of Wolfe, the epithelium is of clear cuboidal type, with large dark nuclei, but

in one of our cases, Fig. 4, the tubules are lined by a lower cuboidal epithelium, with a dark-staining solid nucleus and very little cytoplasm. Meyer mentions that mesonephric-duct epithelium may occasionally be stratified, but he makes no reference to acanthomatous islands, such as we observed in one of our cases, nor has any other author apparently noted these. In addition to such tiny, practically always microscopic, adenomas, other small lesions have been noted which are better spoken of as cystadenomas, and in some of these intracystic papillary growths are seen.

The most important of the cervical mesonephric lesions, though it is a very rare one, is the carcinoma, which may arise from cervical mesonephric vestiges. The first 2 cases were reported in 1902 and 1907, by Robert Meyer, and in these he was able to demonstrate this histogenesis by tracing the continuity of the carcinoma with mesonephric structures above and below the tumor. In the half century since Meyer's first report, a total of only 7 carcinomas of this type had been reported, according to the recent compilation of Huffman, who added a case of his own. To this group we can add the following cases:

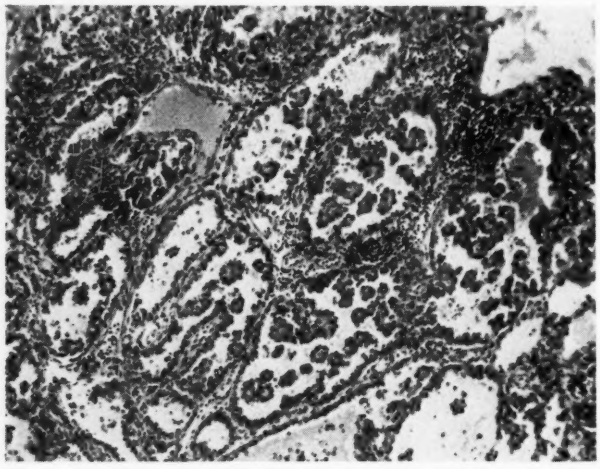

Fig. 5.—Case 3. Gyn. Path. 81508. Cervical adenocarcinoma of mesonephric orgin.

CASE 3.—Gyn. Path. 81508. This patient, a negro woman of 42, was first admitted in September, 1947, because of a uterine myoma, complicated by chronic pelvic inflammatory disease, with a vaginal sinus at the mouth of which there was a tag of granulation tissue. A supravaginal hysterectomy was done, a total being considered technically too hazardous, and the cervix showing no pathology. In January, 1948, the patient returned for treatment of granuloma inguinale and the removal of a benign bladder papilloma. She was next seen in April of 1949, because of a chronic cervicitis, at which time a cervical biopsy revealed a small adenomatous area which at that time was wrongly diagnosed as "papillary adenoma." In retrospect the true nature of the lesion should have been recognized at this time, but this was not done until a second biopsy in September, 1950, showed a lesion of exactly the same type as had been revealed at the first biopsy. A radical removal of the cervical stump and the densely adherent adnexa was then carried out. The ovaries showed no macroscopic or microscopic evidence of neoplasm, but the cervix showed what we interpret as a mesonephric type of adenocarcinoma with a pattern quite identical to

that of the Schiller mesonephroma in the ovary. We believe that this histogenesis is clinched, as it was in Meyer's 2 cases, by the finding of areas of nonneoplastic mesonephric canals leading to what is evidently a benign mesonephric adenoma, and then the mesonephric type of carcinoma.

CASE 4.—Gyn. Path. 106044. This case we are mentioning only briefly, with the kind permission of Dr. D. Strother Pope, of Charleston, South Carolina, to whom we are indebted for the sections, since Dr. Pope expects to make a later full report of the case. The patient was 13, the first symptoms being free bleeding which was thought to be of menstrual nature. A dilatation and curettage showed the cervix to be completely destroyed by the growth, which also infiltrated the vaginal fornix. Laparotomy was done in June, 1953, but hysterectomy was found impossible. The child developed convulsions in September, and shortly afterward died. The autopsy showed both kidneys to be completely blocked off, with extensive lung metastasis also present.

There appears to be no question that this tumor is another instance of mesonephric carcinoma of the cervix. Although there was no involvement of the ovaries, Fig. 6 shows the cervical tumor to have the typical structure of the so-called Schiller mesonephroma of the ovary. Especially striking, however, is the fact that transitions are readily demonstrable to areas in which one sees the typical histology of clear-cell carcinomas. This not only suggests, as we have already emphasized, the close kinship of mesonephroma and clear-cell carcinoma, but their probable common origin from the mesonephric elements in the cervix and/or vaginal fornix.

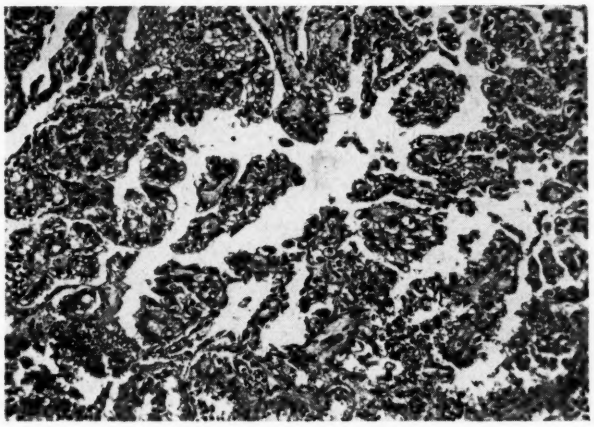

Fig. 6.—Case 4. Gyn. Path. 106044. Mesonephric adenocarcinoma of cervix in girl of 13, with fatal termination. Case of Dr. D. Strother Pope.

Another case which we believe to represent cervical carcinoma of mesonephric origin is the following:

CASE 5.—Gyn. Path. 92519. A white woman of 50 was operated upon in the Department of Surgery in February, 1951, for acute appendicitis. At that time a firm mass was noted in the cul-de-sac, and she was referred to the Department of Gynecology. The mass was almost the size of a small orange, involving the posterior cervix, and being adherent to the rectum, although proctoscopic and x-ray studies excluded a rectal origin. The pars vaginalis and the endocervix were normal. As the woman was 50, a panhysterectomy and bilateral salpingo-oophorectomy were done to give access to the tumor, which was then removed, though incompletely. A section of the tumor is shown in Fig. 7. From this and from what has been said as to the normality of the cervical mucosa, we do not see how one can interpret it as other than mesonephric in origin.

Vaginal Lesions of Probable Mesonephric Origin

From the standpoint of pathologic lesions of probable mesonephric origin it seems that the vaginal fornix could almost be discussed with the cervix, since it is in these two segments of the genital canal that vestigial mesonephric-duct elements apparently show a more frequent proliferative and even neoplastic tendency than in others. We have already spoken of simple mesonephric adenomas of the cervix, and similar benign adenomas may occur, though rarely, in the lateral fornix of the vagina, as demonstrated more than 50 years ago by Meyer. Such benign lesions usually present clinically as ulcers, but an ulcerative form may also be assumed by rare malignant lesions arising from mesonephric elements in this location. On the other hand, mesonephric lesions of the vaginal fornix may be papillomatous and these may likewise be subdivided into benign and malignant groups.

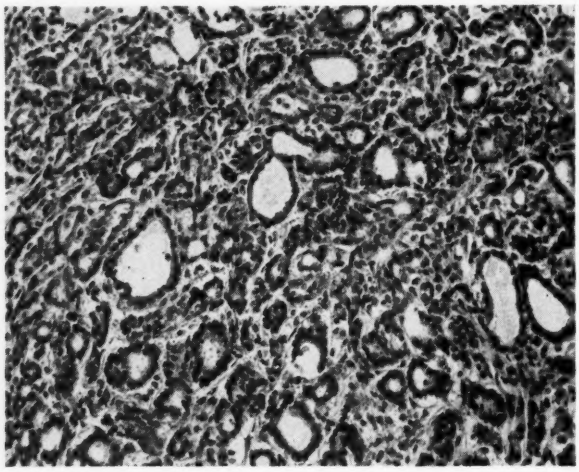

Fig. 7.—Case 5. Gyn. Path. 92519. A third case of mesonephric carcinoma of cervix, patient aged 50. Pars vaginalis and endocervix normal.

Ulcerative Vaginal Lesions

CASE 6.—Path. No. 91439. For the slides of this case we are indebted to Dr. W. P. Jennings of Reading, Pennsylvania, while Dr. E. R. Brubaker, the surgeon, has kindly supplied the clinical and follow-up data. The patient, a nullipara of 24, had no symptoms except postcoital spotting, the source of which was obviously a raised granular area in the lateral fornix of the vagina. In 1950 this was excised, microscopic examination then showing hyperplastic mesonephric tubules in the floor of this ulcerative lesion. Recurrence of ulceration was noted in the fornix in May of 1951, and, after consultation with Dr. Robert Kimbrough, Jr., radical hysterectomy and partial colpectomy were done on June 12, 1951. Microscopic study showed no malignancy, no residua of the original lesion, and no gland involvement. Examination in 1953 showed the patient to be apparently perfectly well. The ulcerative lesion in this case we have interpreted as having its source in a benign adenomatous hyperplasia of mesonephric tubular remnants.

CASE 7.—Path. No. 96981. For the slides of this case and permission to include it in our study we are also indebted to Dr. W. P. Jennings, of Reading, Pennsylvania. The patient was a white woman of 41, with a slowly progressive granulomatous lesion, with a

rather hard base, in the fornix of the vagina. A biopsy had been done 3 years before, with a pathologic report of vaginal adenoma. A total hysterectomy was done because of excessive menstruation, and the vaginal lesion excised. The microscopic appearance is shown in Fig. 8. No other origin than the mesonephric duct seems conceivable for the clusters of tubules and canals, with their lining one-cell thickness of cuboidal epithelium, and with no suspicion of malignancy. We have interpreted this lesion as a benign adenoma of mesonephric origin, quite similar to those reported by Meyer, Wolfe, and Huffman.

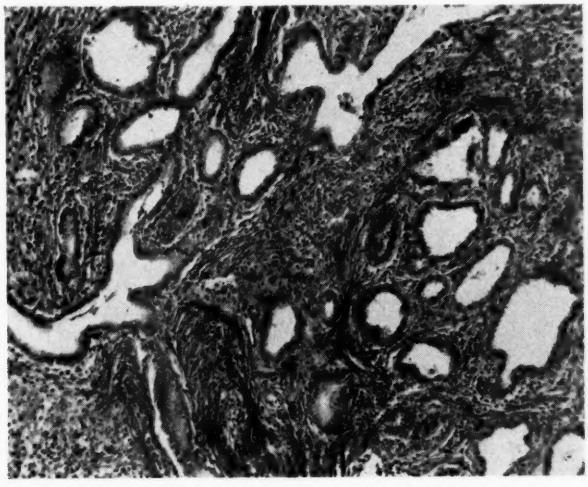

Fig. 8.—Case 7. Gyn. Path. 96981. Benign adenoma of mesonephric origin (vaginal fornix).

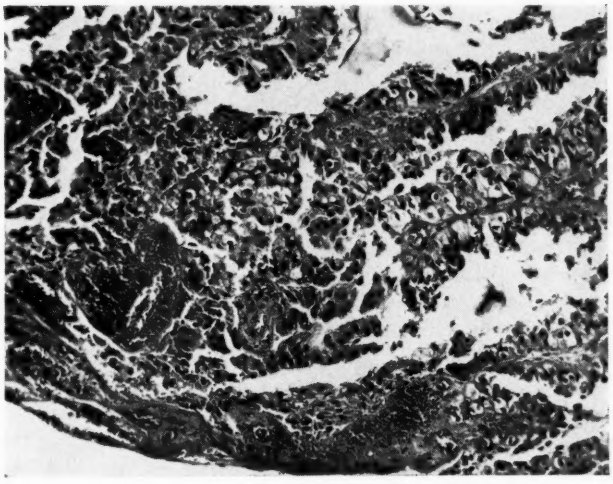

Fig. 9.—Case 8. Gyn. Path. 102002. Mesonephric adenocarcinoma of vaginal fornix.

CASE 8.—Gyn. Path. 102002. The slides and clinical note on this patient were kindly sent to us by Dr. Lester Rauer of Philadelphia. The patient was a white woman of 51, with a large ulcerated lesion of the upper vagina. The only information available is that a curettage and cervical biopsy had been negative and that laparotomy had been done, with total hysterectomy and bilateral salpingo-oophorectomy, but with completely negative findings in so far as any neoplastic disease in the internal pelvic organs or elsewhere in the abdomen were concerned. The microscopic examination of the vaginal lesion showed a

malignant growth of definitely tubular or glandular pattern similar to that of ovarian mesonephroma. Because of this fact, the apparently primary origin in the vagina, the fact that with the rarest of exceptions primary vaginal cancer is epidermoid, and that mesonephric vestiges would seem to be the only conceivable origin for a tubular tumor of this structure, we have classified this tumor as an adenocarcinoma of mesonephric origin.

CASE 9.—Gyn. Path. 104683. For the second case of this category we are grateful to Dr. J. Orde Poynton of Adelaide, South Australia, who sent us not only the sections, but also clinical and follow-up notes. The lesion in this 34-year-old patient was situated in the lateral vaginal wall and was considered to be an adenocarcinoma, so that a total hysterectomy and vaginectomy were done. Incidentally, the uterus was bicornuate. The microscopic appearance of the vaginal tumor, as shown in Fig. 10, is identical with that of the Schiller type of ovarian mesonephroma, and we believe that this vaginal adenocarcinoma is of mesonephric origin. Dr. Poynton reports that as of Jan. 4, 1954, the patient has had no recurrence.

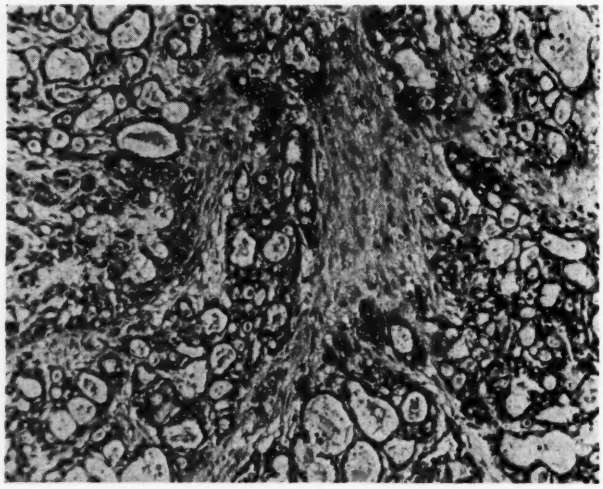

Fig. 10.—Case 9. Gyn. Path. 104683. Adenocarcinoma of what we believe to be mesonephric origin in lateral vaginal fornix. Patient aged 34.

CASE 10.—Gyn. Path. 88949. For the slides of this case and permission to include them in our paper we are grateful to Dr. C. W. Davey, Gloucester, England. The patient was 76, with a history of vaginal bleeding for 1 month. The examination showed a cystic swelling 3 inches in diameter behind and attached to the cervix. Athough the cystic mass was found at operation to be the body of the uterus, the topography appears to have been rather confused, and the microscopic appearance of the lesion at least suggests the possibility of cervical origin. It shows a fairly typical clear-cell appearance, unlike any ordinary type of uterine carcinoma, but quite similar to some of the apparently mesonephric tumors we have described. It is of interest that at least one of the British pathologists who examined slides of this tumor, Dr. C. Taylor of Birmingham, is quoted by Dr. Davey as saying that the lesion "is similar to the clear-cell carcinoma resembling hypernephroma."

Papillary Vaginal Lesions

Among the probably mesonephric vaginal lesions in our series we have considered especially interesting a group in which the lesion assumed a very papillomatous architecture, and which were actually so grapelike as to simulate sarcoma botryoides clinically, in spite of the fact that there is not the

slightest microscopic resemblance to the latter. Since it is in infants and very young children that one is most likely to find sarcoma botryoides, and since the latter, in spite of its rarity, is still not as rare as the grapelike papillary mesonephric lesions, one can understand that when the latter occurs in infants, as in one of our patients, sarcoma botryoides would be the natural clinical suspicion.

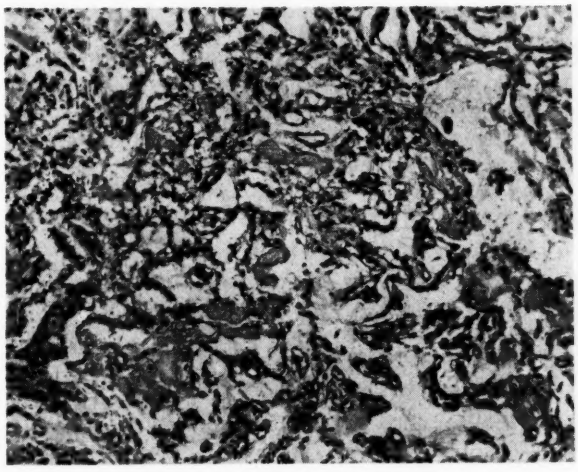

Fig. 11.—Case 11. Gyn. Path. 104183. Papillary grapelike tumor of upper vagina in infant of 15 months, with rapidly fatal termination.

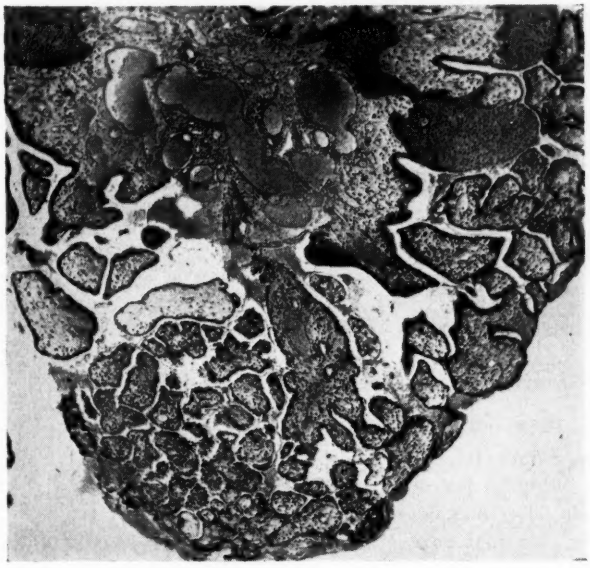

Fig. 12.—Case 12. Gyn. Path. 107833. Papillary tumor of upper vagina which we believe to be of benign mesonephric origin, in infant of 14 months.

CASE 11.—Gyn. Path. 104183. For the slides and data of this case and permission to mention it briefly in this paper, we are indebted to Drs. J. J. Kilbury, J. W. Hawley, W. S. Orr, and R. A. Ross of Little Rock, Arkansas. The patient, an infant of 15 months, was admitted Nov. 22, 1952, because of inability to void and vaginal bleeding from a

grapelike tumor appearing to arise from the upper part of the vagina. Only palliative measures were possible, and the patient's condition deteriorated rapidly, with death on Jan. 10, 1953. At the autopsy, of which a full note was sent by Dr. Ross, the pelvis was found full of the tumor tissue, with numerous metastases to distant organs. The details are here given only very briefly, since the case is to be more fully reported later by Dr. Ross.

CASE 12.—Gyn. Path. 107833. This patient was observed by Dr. Kurt Weidenthal of Hudson, Ohio, to whom we are grateful for permission to make brief mention of it here, as well as for the pathologic material and the clinical information. The patient was an infant of 14 months who had several episodes of slight vaginal bleeding. In March, 1953, the mother reported that a liverlike substance protruded from the vagina, and examination on March 27 confirmed the presence of a liverlike granulating protrusion. A biopsy of this mass showed the picture depicted in Fig. 12 and on May 5 under general anesthesia, Dr. Gibson, of Akron, excised what grossly resembled a cervical polyp, though the sections indicate that it probably arose from the vaginal vault. Dr. Weidenthal reports that the patient on Dec. 14, 1953, was apparently entirely normal, with consistent gain in weight and height.

The section shows a very strikingly papillomatous lesion arising from what is apparently the vaginal wall, segments of normal vaginal stratified epithelium being directly continuous with the tumor. The papillary pattern is of rather substantial structure. The stroma is a light textured and very vascular connective tissue, and the covering epithelium of the papillae is of a low cuboidal and in some areas a hobnail or peglike type, exactly like that seen in many cases of ovarian mesonephroma. Our diagnosis was benign mesonephric papilloma of the vagina.

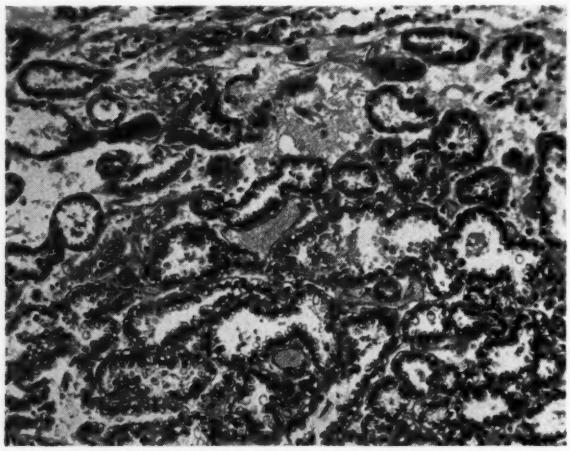

Fig. 13.—Case 13. Gyn. Path. 97748. Multiple polypoid lesion of upper vagina and cervix, described as grapelike and friable. Patient aged 20.

CASE 13.—Gyn. Path. 97748. The sections of this case were sent to us from St. Luke's Hospital, Bethlehem, Pennsylvania, with the note that the patient was a white woman of 21, with a multiple polypoid lesion involving the vaginal fornices and apparently also the cervix. The lesion is described as grapelike and friable.

Microscopically, we feel sure that a glance at Fig. 13 would at once compel the diagnosis of Schiller mesonephroma of the ovary if one did not know its vaginal source, so perfect is the similarity in the tubular pattern and the characteristics of the epithelium. Not only is this true, but in many areas the epithelium shows transitions to the clear-celled, rather glassy-looking epithelium of clear-cell carcinoma, much like those which have already been described in the ovary. The coexistence of the clear-cell tumor elements and those of the Schiller mesonephroma with transitions between the two strongly indicates, as we have previously discussed, a common origin from mesonephric vestiges.

Summary

In this paper we have tried to present evidence as to the probable mesonephric histogenesis of a group of rare and widely separated pelvic lesions. These comprise two types of ovarian tumors, a few solid broad ligament tumors, certain rare instances of cervical adenocarcinoma, and a small group of ulcerative or papillary vaginal lesions, either benign or malignant. There is still such a woeful lack of exact knowledge of the sequential histologic characteristics of the pronephrosis, mesonephros, and metanephros that no one is justified in any arbitrariness of viewpoint on such a question as this. Our studies lead us to believe, however, much more strongly in the mesonephric origin of the Schiller mesonephroma than we formerly did, and also in its close histogenetic kinship with the so-called clear-cell carcinoma of the ovary. One reason for this is their not infrequent coexistence in one tumor, either ovarian or in some mesonephric area such as the cervix and vaginal fornix.

The fragmentary remnants of the mesonephric structure which may persist in the cervix and the vaginal fornix may give rise to carcinoma of otherwise baffling nature, and we have added 3 cases of this sort to the 8 previously collected by Huffman. Certain ulcerative and papillary lesions of the vaginal fornix may develop from mesonephric rests, though they are exceedingly rare. We have recorded a small group of these and have emphasized that the papillary variety has often occurred in children, like sarcoma botryoides, which it may resemble clinically, though there is not the slightest resemblance between the two lesions from the standpoint of microscopic structure. In our group of ulcerative lesions of the vaginal fornix which we have interpreted as of mesonephric histogenesis, 2 have been benign and 3 malignant. Finally, we have described 3 mesonephric papillary lesions, 2 malignant (ages 15 months, 21 years) and 1 benign (age 14 months).

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Discussion

DR. EDWARD C. HUGHES, Syracuse, N. Y. (By invitation).—The authors have presented evidence which tends to confirm the claims made first by Robert Meyer and later by others whom they have mentioned in their manuscript, namely, that some pelvic tumors are of mesonephric origin. The material which has been presented today has been accumulated from wide sources and has been meticulously analyzed. Some may think that they have drawn the line perhaps too thin merely because of the fact that the reproductive and urinary organs both have mesodermal ancestry. The groups of cases which they have presented are very selective. They have emphasized two types of tumors of the ovary: the Schiller mesonephroma and the clear-cell carcinoma which may arise from these sources. They have stated that these types may occur singly or together in the same lesion. This leads to possible speculation as to the time of embryologic formation. There are certain embryologic relationships which may explain these possibilities.

The genital mass develops later than the mesonephric structure and, at first, is formed on the medial aspect of the middle one-half of the duct. As the genital gland grows, it displaces the nephrogenic duct laterally, and the ovary comes in direct contact with the units of Bowman's capsule and the collecting mesonephric tubules as they bend to form the secreting tubules. This early development may cause these primitive glomerular tufts and the nephrogenic tubules to become displaced into the substances of the genital gland. Fragments, or even the entire glomerular tuft, may be found in the ovary, a point which Schiller has strongly emphasized and which has been debated by some of his adversaries. Failure to find these endothelial radicals should not rule out this type of tumor, provided nephrogenic tubules are present.

A possible explanation of the failure to find these glomerular tufts within these tumors may be as follows: The mesonephric structure extends from the fourth cervical to the third lumbar segment at the 5 mm. stage. It undergoes a series of modifications which proceeds in a craniocaudal direction. Degeneration particularly occurs along the entire duct. This degeneration is partly in the nature of a dedifferentiation and results in the extrusion of the capillary tufts from their glomeruli. There is a physiologic basis for this, founded on the fact that prior to degeneration of the tubules, the blood flow to the tuft has stopped. If the ovary should encroach upon the nephrogenic duct after the extrusion of these capillary tufts in this particular segment of the duct, it is possible that they might or might not be incorporated within the ovary and are not found when tumor formations have been completed.

The second type of ovarian tumor—the clear-cell carcinoma—may also mean that these lesions have developed at a later embryologic age. While the ovary is forming, it is held at the caudal aspect of the embryo by the ovarian ligament which is the remains of the gubernaculum. The metanephric structure, which is an offshoot of the nephrogenic duct at a lower level, accumulates tubules from the nephrogenic cord and proceeds in a cranial direction to become the definitive kidney. It is possible that it may come in close contact with the ovary during its ascent. These facts may be the basis for the clear-cell carcinoma which is found in both the ovary and the kidney.

It seems logical, owing to the length of development of the nephrogenic duct, that remnants may persist particularly in the fetal cervix which is much longer than the uterine body in early life. It is also possible for the nephrogenic cell to be located in the broad ligament and upper portion of the vagina. Even though degeneration occurs along its entire length, remnants of this structure should give rise to tumors in these various locations.

Searching through the material of the Pathological Departments of the Medical School and Syracuse Memorial Hospital rewarded us with findings of one mesonephroma, three clear-cell carcinomas of the ovary, several clear-cell carcinomas of the cervix, and incidentally several carcinomas of the prostate that appear to be clear cell in character. These tumors will be reported more in detail by Dr. John Prior at a later date. Although it seems improbable that these tumors of the prostate are similar to those found in the ovary, they were clear cell in character. These were noted particularly after the patient

had been given large doses of estrogen. Although the prostate is almost entirely endodermal in origin, there has been some discussion that possibly the posterior wall of the prostatic urethra may be mesodermal in origin. It is interesting to note that most tumors of the prostate develop in this area. If this is true, it is possible that tumors of clear-celled character could arise in this gland in the male.

I wish to present four cases. This mesonephroma was found by pelvic examination in a 54-year-old woman. Grossly the left ovary measured 15 by 8 by 7 cm., was solid pinkish yellow in color, and possessed an intact external capsule. The cut surface was gelatinous and myxomatous in character and there were scattered areas of hemorrhage thoughout. Microscopically, the tumor was composed of many tubules of nephrogenic character. These tubules were lined with a low cuboidal type of cell, and some possessed the typical hobnail type of cell. There were a few structures that appeared like immature glomerular tufts. This patient has been lost to the service and the follow-up has been impossible.

The three other ovarian tumors which were classified as clear-cell carcinomas very closely resembled the hypernephroma of the kidney. Foote presented a series of 75 kidney tumors and has shown that the greatest majority could be classified as true hypernephromas of the kidney. The histologic arrangement, appearance, and character of the tumor cells in the kidney and the ovary were quite similar. Histochemical stains for mucin and glycogen showed that clear-cell tumors of the kidney as well as of the ovary failed to show mucin and there was an absence of glycogen. The clear-cell tumor of both the ovary and the kidney possesses granules of fat which may be indicative of cellular degeneration.

The authors have not quoted specifically the survival rate in individuals with tumors of this character. Foote has stated that 45 per cent of those who have true hypernephroma of the kidney have survived longer than a five-year period. It is also interesting that these three patients with clear-cell carcinoma have lived five years or longer, although one has developed a metastatic node in the neck four years after the original surgery. I would like to present these cases briefly:

Case No. CIH 48-466 was a 48-year-old woman who developed a ripidly increasing tumor in the lower abdomen over a period of three months. The tumor measured 15 cm. The external surface was smooth with a multiloculated interior and there was one soft pink nodule which measured 3.5 cm. Only the diseased ovary was removed. Microscopic section revealed that the tumor was made up of large clear epithelial cells resembling a hypernephroma of the kidney. The patient is alive and well six years after the surgery.

Case No. 44-2863 was a 44-year-old woman who had a mass in the abdomen that increased in size over a period of six months. The mass, on removal, measured 12 cm.; it had a smooth external surface and was made up of many papillary nodules measuring from 0.5 to 4.0 cm. in diameter. There was hemorrhage throughout. One ovary alone was removed and this was followed by irradiation. Follow-up showed the patient to be alive eight years after the surgery. She has not been seen since 1952.

Case No. 50-4543 and 54-568 was a 55-year-old woman who noticed a gradual increase in the size of the abdomen. The original tumor of the ovary on removal measured 23 by 20 by 12 cm. The external surface was smooth. The tumor was lined with yellow material which was papillomatous in character. The contents were thick and yellow. The endometrial cavity of the uterus was filled with a yellow cheesy material extending into the endocervix which was diagnosed as adenoacanthoma. A total hysterectomy was performed. The patient appeared well four years after the surgery except for a metastatic node which had developed in the neck. Microscopic appearance of this gland was identical with the ovarian tumor removed four years previously.

The authors, Drs. Novak, Woodruff, and Novak, have presented by their careful examination strong evidence substantiating the concept that the nephrogenic duct may be the origin of certain histologically typical tumors which may occur in the female genital organs.

DR. GEORGE H. GARDNER, Chicago, Ill.—We are flattered that the essayist has used the anatomically and embryologically correct terminology which we have advocated in referring to the *mesonephric* origin of these tumors.

My comments will be restricted to findings in the cervix. The first slide presents a diagrammatic sketch of our concept of the course of the mesonephric vestigial remnants in the cervix, where it is not just a simple tubule but manifests arborizations in the ampullar portion. Such remnants may be found in routine blocks, especially those from the lateral portions of the cervix, and it is sometimes quite difficult to be certain whether one is dealing with simple vestigial remnants or with an adenoma of the mesonephric duct.

In addition we have found three adenocarcinomas of the cervix which were derived from the mesonephric duct and one of these was not recognized clinically as a cancer because the contour of the cervix was maintained; it was covered by smooth intact epithelium; and the lesion was confined to the musculature. Since the tubules, canaliculi, and duct-like structures were almost filled by proliferating epithelium, it is obvious that this was an adenocarcinoma; the patient died eventually of her cancer, although not for some seven years after this specimen had been obtained.

DR. J. DONALD WOODRUFF, Baltimore, Md. (By invitation).—The infrequence of true tumor development has been recognized by the few cases recorded in the literature, as noted by Dr. Novak, and the few we have added today. However, the presence of adenomatous vestiges is more common than is recognized. The inability to recognize these are vestiges and not true neoplasm has led to serious errors in diagnosis. A case we have seen recently will demonstrate this fact. The slide is from a biopsy of the cervix taken in our clinic about six weeks ago. This patient had no gross lesion, as is usually the case. This particular section suggested carcinoma to one observer. Most of us felt it represented an example of mesonephric vestiges in the cervix. Furthermore, this section demonstrates the fact that such remnants can occur so close to the portio as to be obtained by the biopsy clamp. Stratified epithelium was present in this same fragment of tissue. Finally, this slide demonstrates the fact that sometimes squamous metaplasia occurs in the adenomatous vestiges.

The second case showed a similar picture. We did not see the sections until some months after amputation of the cervix and vaginal repair. The patient was 34 years old and, because of finding a pattern similar to the above, she was subjected to ray therapy, both radium and deep x-ray, with resultant fistula, which produced the usual disability. Sections from the cervix again demonstrated a picture which we consider to be entirely benign, and representative of remnants of mesonephric tubules.

DR. EDMUND R. NOVAK, Baltimore, Md. (Closing) (By invitation).—It seems that we must recognize these mesonephric-duct tumors as a real and distinct pathological entity. On the other hand, it may be worth noting that occasionally we find them in conjunction with other types of adnexal lesions. A recent study by Dr. Woodruff and myself revealed this pattern to be present in about 8 per cent of all papillary serous tumors. I wish to show a slide to illustrate this variant.

This tumor (OTR 339) is classified as a papillary serous cystadenoma, and four out of the five submitted sections show a very typical pattern. However, on the basis of a few areas represented by this lantern slide, one member of the Ovarian Tumor Registry made a diagnosis of mesonephroma, and one other member mentioned this possibility, but it was finally categorized as a papillary serous tumor. In our recent survey of some 90 cases, we found 6 or 8 generally typical papillary serous tumors showing such diverse areas as this. I think you can readily see many clear-cell areas with other typically mesonephric features such as a tubular pattern lined by a characteristic low cuboidal cell with peglike projections into the lumen of the tubules.

Frankly, we do not know just why this should be, but it does not resemble a degenerative process. I suppose it could represent some type of metaplastic phenomenon, but we wondered if, in addition to stimulation of the germinal epithelium with resultant papillary serous tumor formation, the immediately adjacent mesonephric-duct elements might not receive some similar impetus. I repeat that we do not really know why, but unquestionably this histological admixture can occur with the papillary serous and perhaps other types of ovarian tumors.

THROMBOEMBOLIC DISEASE COMPLICATING PREGNANCY AND THE PUERPERIUM*

JOHN C. ULLERY, M.D., PHILADELPHIA, PA.

(From the Philadelphia Lying-In Division of the Pennsylvania Hospital)

THE occurrence and serious results of thromboembolic disease in obstetric patients constitute some of our most challenging problems. Throughout the history of childbirth physicians have been acutely aware of the tendencies toward hemorrhage and thrombosis during pregnancy or after delivery.

Until recently little could be done for thrombosis except to observe with respect and humility the devastating effects of this disease in the living patient or at the autopsy table. In the past few years the development of new laboratory methods, the discovery of anticoagulant drugs, and improved surgical techniques have provided us with the tools to investigate in greater detail the mechanism of thromboembolic disease in pregnancy, and to prevent and treat it with greater success than was formerly believed possible.

The purpose of this presentation is to review the mechanism of thromboembolic disease in pregnancy and the puerperium and to analyze the cases treated at the Philadelphia Lying-In Division of the Pennsylvania Hospital, Philadelphia, Pennsylvania, for a twenty-year period, 1933-1953. The study is divided into three parts:

THROMBOEMBOLIC DISEASE IN PREGNANCY AND THE PUERPERIUM:

I. Thrombus Formation in Relation to Pregnancy.
1. Mechanism.
2. Etiology.
3. Classification.

II. Antepartum Thromboembolic Disease.
1. An analysis of the literature and cases treated at the Pennsylvania Hospital, 1933-1953.

III. Postpartum Thromboembolic Disease.
1. Analysis of 172 cases treated at the Pennsylvania Hospital, 1933-1953.
2. Methods of treatment.
   a. Prophylactic.
   b. Active.

I. Thrombus Formation in Relation to Pregnancy

1. Mechanism.—

An understanding of the basic concepts of the mechanism of intravascular clotting, together with the recognition of certain predisposing fac-

*Presented by invitation at the Seventy-seventh Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 20, 21, and 22, 1954.

tors, is indispensable to the clinician if he is to be aware of and treat the processes occurring in his patient with this disease.

The control of thromboembolism is based upon an understanding of the physiology and pathology that lead to the formation and propagation of a thrombus or clot in the vein.

The exact mechanism of intravascular clotting and venous thrombosis is unknown. Many theories have been advanced, but none has been completely acceptable in answering all the problems of coagulation in the human body. Extensive research has shown the clinical and physical properties of in vitro clotting to be well understood, but in vivo intravascular clotting still remains an enigma.

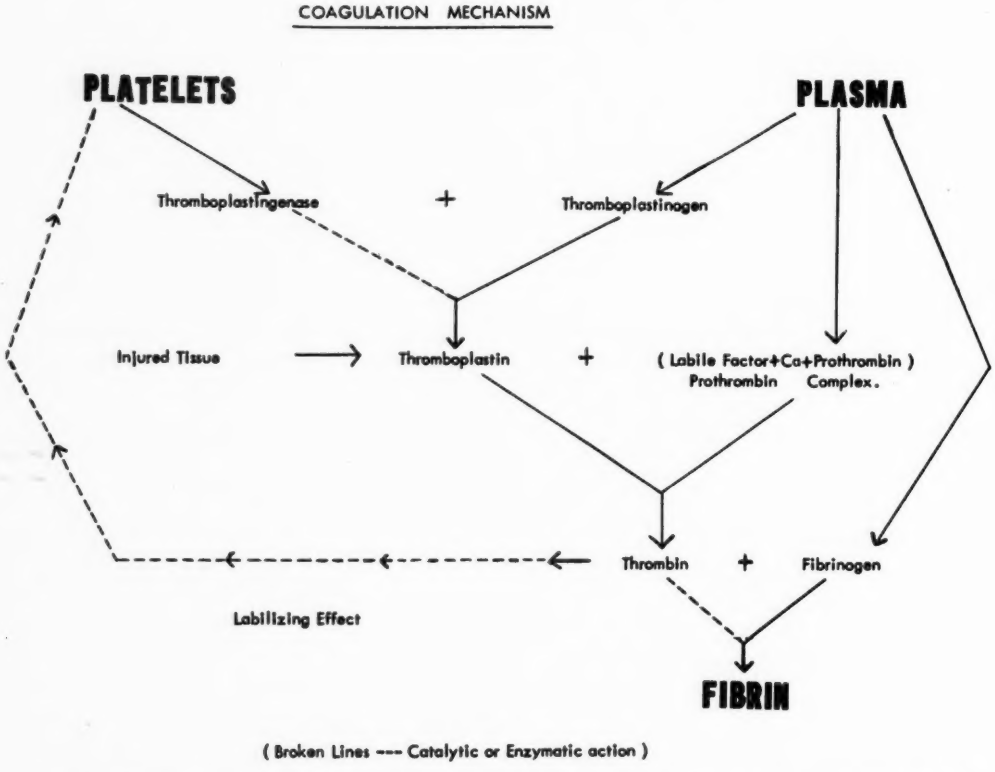

Fig. 1.—The coagulation mechanism. (Modified from Quick, A. J.: Surg., Gynec. & Obst. 91: 296, 1950.)

Figs. 1-3 by permission of *Surgery, Gynecology and Obstetrics.*

Stefanini in 1953 showed that most investigators are in accord on certain basic principles of the coagulation mechanism. These are shown in Fig. 1. Although not complete, the diagram modified from Quick's presentation explains these principles and aids in an understanding of the process of venous thrombosis; it also formulates a rational basis for therapy in thromboembolic disease. It may be seen that the platelets and plasma are the two main constituents of the blood that produce fibrin or coagulation in the presence of disease, injury, or abnormality of the vascular endothelium. The vital step

in the mechanism is the production of thrombin. When platelets adhere to the surface of the abnormal endothelium, they rupture or disintegrate and liberate thromboplastingenase which activates the thromboplastinogen of the plasma to form thromboplastin. The action of thromboplastin on the prothrombin complex of the plasma forms thrombin. As the thrombin combines with fibrinogen to form fibrin or the end product of coagulation, a chain reaction occurs from the labilizing effect of thrombin on the platelets. The absorption of thrombin to fibrin is the primary factor in the control of the chain reaction. Thrombin, because of its action on platelets, has the power to set off a chain reaction that potentially could coagulate all the fibrinogen and convert all the circulating blood into a solid clot. Because of the

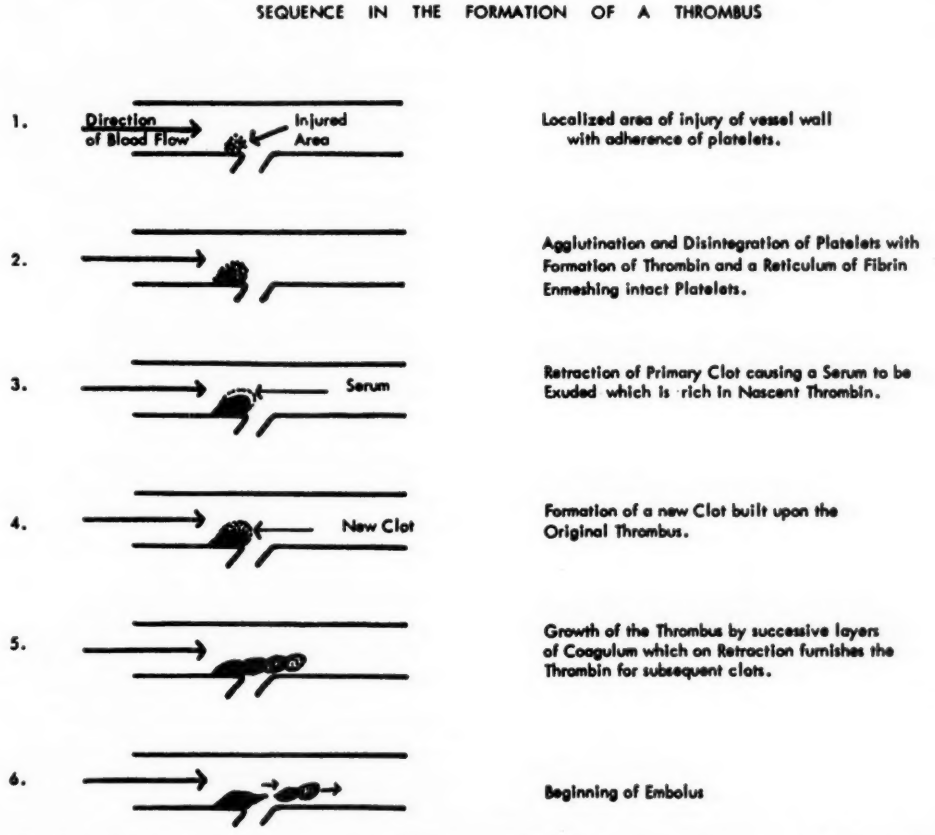

Fig. 2.—Sequence in the formation of a thrombus. (Modified from Quick, A. J.: Surg., Gynec. & Obst. 91: 296, 1950.)

enormous surface of the fibrin reticulum in the clot, however, the thrombin is promptly removed by absorption, and because of this mechanism together with antithrombin, the chain reaction cannot be initiated.

With this theory of hemostasis, or the coagulation mechanism, the problem of thromboembolic disease can be analyzed. Since coagulation necessitates disintegrating platelets as the initial cause, the following sequence occurs in the formation of a thrombus (Fig. 2 modified from Quick): (1) a localized

area of injury of a vessel wall with adherence of platelets, (2) agglutination and disintegration of platelets with formation of thrombin and a reticulum of fibrin enmeshing intact platelets, (3) retraction of the primary clot, causing a serum to be exuded which is rich in nascent thrombin, (4) formation of a new clot built upon the original thrombus, (5) growth of the thrombus by successive layers of coagulum which, on retraction, furnishes the thrombin for subsequent clots, (6) beginning of embolus.

Thus it can be seen that, if the circulation is rapid, the serum is promptly washed away and the thrombus fails to propagate. When the circulation is sluggish, the exuded serum causes the clotting of blood about the thrombus, and a new clot is built on the old thrombus. It in turn retracts, and fresh serum brings an additional extension of the thrombus.

Because of the flow of blood, the growth of the clot is principally at the tip and in the direction of the blood stream. Thus the retraction of the clot explains why the thrombus propagates itself and accounts for the observation that the clot may be entirely unattached to the walls of the vessel except at the point of origin. Such a clot is called the phlebothrombolic type.

Of greatest significance in the treatment of thrombophlebitis and phlebothrombosis is the clot retraction that occurs in the thrombus. On it depends first, the growth of the thrombus, and, second, the shrinking of the propagating mass which prevents it from staying in contact with the vessel wall. It is influenced by (1) the number of circulating platelets, (2) the speed and quantity of thrombin production, and (3) the cell volume of the blood.

Thus the logical approach to the prevention or treatment of venous thrombosis is either to reduce the clot retraction in the blood, by lowering the number of circulating platelets, or to regulate the production of thrombin. The former cannot be accomplished as yet, for too little is known about influencing the number of platelets. For the second approach we have several therapeutic agents which regulate the production of thrombin: heparin, Dicumarol, Tromexan, and Danilone (Fig. 3).

Heparin acts as an antiprothrombin as well as an antithrombin. Dicumarol, Tromexan, and Danilone reduce the production of thrombin by lowering the prothrombin level of the blood. Any reduction of thrombin formation lowers the clot retraction, and therefore the thrombotic tendency.

The third factor which influences clot retraction, the cell volume of the blood, is mechanical. The greater the number of cells the larger the bulk of the nonretractile part of the clot. Thus it can be seen that clot retraction is accelerated and more pronounced in anemic than in normal blood.

The whole process of intravascular clotting and thrombus formation is enormously complex and many changes (chemical, physical, physiological, and pathological) are taking place at the same time. If these previously mentioned basic concepts are known to the clinician, progress in therapy can more logically be made.

2. Etiology.—

In addition to this mechanism of thrombus formation, certain predisposing factors are known. For instance, anesthesia, infection, and nutritional de-

ficiencies cause increased blood platelet agglutination. Bacterial toxins and histamine production not only cause platelet agglutination but, in addition, stimulate thrombopoiesis and thus increase coagulative tendencies by increasing fibrinogen, prothrombin, and platelets.

Also included as etiological agents are trauma to blood vessels, stasis, increased viscosity due to dehydration, and absorption of large amounts of substances from damaged tissues. Thus it is not surprising to find that thromboembolic disease is encountered in obstetric patients, as they frequently meet these predisposing requirements. In the puerperium immobility of the lower extremities, the wearing of tight abdominal binders, pressure on the popliteal spaces from improperly designed leg holders, all increase the possibility of intravascular clotting. Obesity, anemia, hemorrhage, dehydration, and the presence of infection also may contribute to the danger of thrombosis.

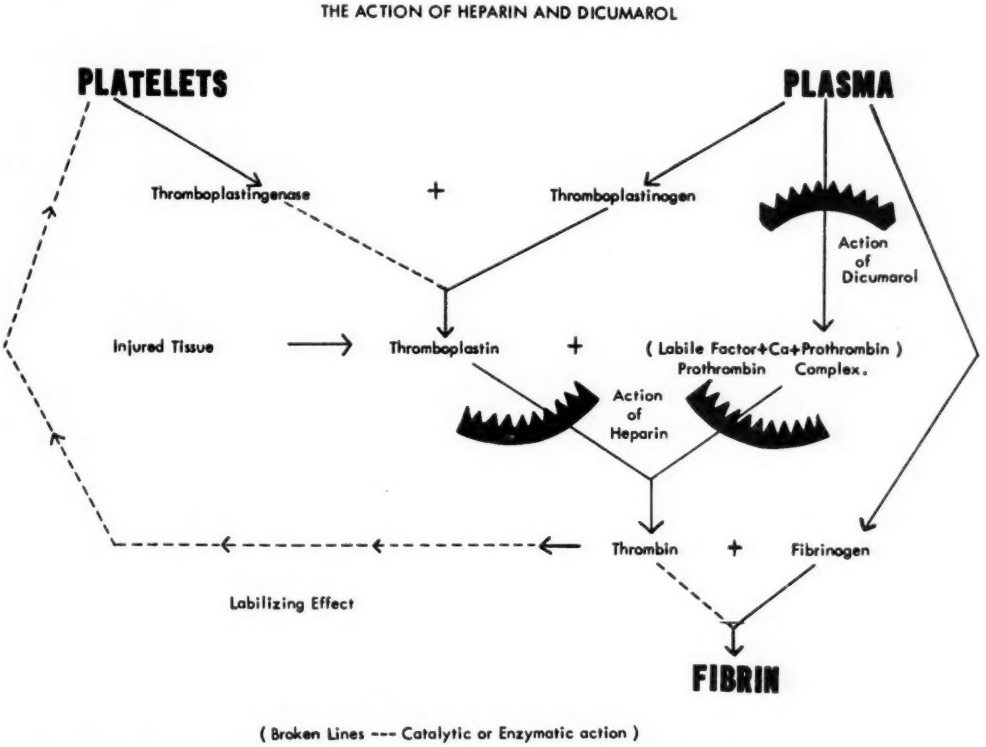

Fig. 3.—The action of heparin and Dicumarol upon the coagulation mechanism. (Modified from Quick, A. J.: Surg., Gynec. & Obst. 91: 296, 1950.)

3. Classification.—

We have classified our cases of antepartum and postpartum thrombosis in the twenty-year period of 1933-1953 as follows:

I. Adherent or obstructing thrombophlebitis.

II. Silent or nonobstructing thrombophlebitis (phlebothrombosis).

III. Septic thrombophlebitis.

Associated with pelvic sepsis in septic abortion or puerperal sepsis. Not included in our series except if complicating puerperal sepsis.

IV. Superficial thrombophlebitis.

Occurs in varicose veins of leg or vulva. Not included in our series.

II. Antepartum Thromboembolic Disease

1. Analysis of the Literature and Cases Treated at the Pennsylvania Hospital, 1933-1953.—

The occurrence of obstructive thrombophlebitis or phlebothrombosis as a complication of the antepartum period is apparently rare. Available figures vary from 0.037 per cent to 0.1 per cent. The frequency is difficult to ascertain, as most of the records do not mention the number of antepartum patients involved. A review of the literature to date reveals 126 cases of antepartum thrombosis. Probably more cases do occur but are not reported. If all pregnancies with this complication were reported, better assessment of therapy could be made for differences of opinion as to the conservative, surgical, or anticoagulant treatment affect the prognosis in such cases.

In addition to these 126 collected cases of antepartum thrombosis, a study of our records from 1933 to 1953 revealed 9 patients with this disease. These nine instances occurred in 50,332 patients seen during pregnancy and delivered in the hospital, an incidence of 0.018 per cent. Seven were not treated with anticoagulants and, of these, 2 developed pulmonary embolism and died. Two patients were treated with anticoagulants successfully, one in the third month of pregnancy and the other in the eighth month. Both were delivered at term without further complications, and their babies were living and well with no evidence of hemorrhage.

TABLE I. ANTEPARTUM THROMBOEMBOLIC DISEASE, PENNSYLVANIA HOSPITAL, 1933-1953

PATIENT	YEAR	DURATION OF PREGNANCY AT ONSET OF THROMBOSIS	LOCATION OF THROMBOSIS	PULMONARY EMBOLUS	THERAPY	CONDITION OF BABY AFTER DELIVERY
K. B.	1937	32 weeks	Left femoral-iliac veins	0	Heat, elevation	Living
E. B.	1938	32 weeks	Right femoral veins	0	Heat, elevation	Living
R. K.	1939	39 weeks	Left popliteal veins	0	Heat, elevation	Living
D. G.	1942	36 weeks	Right femoral veins	1 after delivery	Heat, elevation	Living
M. B.	1943	24 weeks	Left femoral veins	0	Heat, elevation	Living
M. F.	1946	16 weeks	Left saphenous	1 (fatal) after term delivery	Ligation at sixteenth week	Living
H. I.	1949	36 weeks	Left femoral and popliteal	0	Heparin 210 mg.; penicillin 12,500 units	Living
M. C.	1949	11 weeks	Left femoral and iliac	0	Heparin 550 mg.; Dicumarol 2,150 mg.	Living
R. M. (unreg.)	1951	38 weeks	Bilateral femoral and iliac	1 (fatal) ½ hour after admission	None	Dead

Of the 135 cases of antepartum thrombosis reviewed in the literature (including 9 of our own) 97 were not treated with anticoagulants. Among the 97 patients not treated with anticoagulants there occurred 18 cases of pulmonary embolus with 15 fatalities, a maternal mortality of 15 per cent.

TABLE II. ANTEPARTUM THROMBOEMBOLIC DISEASE NOT TREATED WITH ANTICOAGULANTS

AUTHORS	YEAR	NO. OF CASES RECORDED	CASES WITH PULMONARY INFARCTS	FATAL EMBOLI
Remy	1922	3	3	3
Holzmann	1924	10	1	1
Knauer	1927	4	4	4
Bansillon and Pigeaud	1931	1	0	0
Laffont and Schebat	1932	1	1	1
Friedlander	1936	1	0	0
Rochat	1939	2	1	1
Faureau	1939	1	0	0
Simard	1939	6	0	0
Maxwell	1939	1	0	0
Walsh and Barone	1947	3	1	1
Nyklicek	1948	1	1	0
Donaldson	1950	48	3	2
Davis	1951	2	0	0
Hallum and Newham	1951	5	1	0
Thornton	1951	1	0	0
Ullery	1954	7	2	2
Total		97	18	15 (15%)

Thirty-eight cases were found in the literature in which anticoagulants were used. Although 7 of these 38 treated patients had pulmonary embolism prior to anticoagulant therapy, there were no fatalities.

TABLE III. ANTEPARTUM THROMBOEMBOLIC DISEASE TREATED WITH ANTICOAGULANTS

AUTHORS	YEAR	NO. OF CASES RECORDED	CASES WITH PULMONARY INFARCTS	FATAL EMBOLI
Yahr, Reich, and Egger	1945	2	0	0
Green and Loewe	1947	1	0	0
von Syndow	1947	1	0	0
Felder	1949	2	0	0
Sachs and Labate	1949	1	1	0
Weiss and Turner	1949	1	0	0
Adamson, Weaver, and Jaimet	1950	5	1	0
Davis	1951	1	0	0
Thornton	1951	2	0	0
Ware	1951	3	0	0
Wright, H. P.	1951	10	2	0
Mansell	1952	5	1	0
Flood	1953	2	2	0
Ullery	1954	2	0	0
Total		38	7	0

The data on the treatment of antenatal thrombosis obtained from the literature and from our experience with 9 cases are too few to draw absolute conclusions on any given method of therapy. The fact, however, that among 97 cases of antepartum thrombosis not treated with anticoagulants there were 15 fatal emboli (15 per cent) indicates the serious consequences that may occur. In the 38 patients in the literature with antenatal thrombosis who had

anticoagulant therapy no fatal embolism occurred. These figures, though small, are statistically significant, indicating that this method of treatment is of benefit in reducing fatalities. It seems most logical to provide the antepartum patient with the benefits of anticoagulant treatment provided the risk of hemorrhage to mother and child is not too great.

We believe the effects of anticoagulants on the mother and child are minimal and safe if the prothrombin time of the patient is maintained within safe limits of 18 to 23 seconds (20 to 30 per cent of normal) regardless of the stage of pregnancy at which the drug is used. In Case 8 (M. C.) of our group, heparin and Dicumarol were given at 11 weeks of pregnancy and within a few days after vaginal bleeding due to threatened abortion. Although the drugs were used in the most critical stage of the life of the fetus, no deformities or hemorrhagic tendencies occurred, either in the remaining portion of the antenatal period, at term, or after delivery.

In Case 7 (H. I.) the patient was on controlled heparin therapy for thrombosis at the time of the onset of labor. There were no untoward effects on the mother or baby during delivery or in the puerperium.

It should be emphasized that vigilance must be unending, with careful regulation of prothrombin times and constant supervision and observation. In this capacity, the cardiologist-internist and the vascular surgeon of the hospital see all such patients in consultation with the obstetrician, to determine the treatment which seems most suited to the individual patient. This teamwork has been of inestimable value.

III. Postpartum Thromboembolic Disease

Obstructing thrombophlebitis and nonobstructing venous thrombosis (phlebothrombosis), although rare during pregnancy, are more frequent after delivery. They may be the cause of severe and prolonged disability or a precursor of pulmonary embolism. These thromboembolic diseases may be precipitated in the puerperium as follows: (1) spontaneously with no known cause; (2) following febrile disease or infections; (3) following operative obstetrical procedures; (4) following trauma.

In the silent or nonobstructing thrombophlebitis (phlebothrombosis) relatively few clinical manifestations may occur. This is more dangerous than obstructive thrombophlebitis because embolic phenomena occur more readily. Indeed, it may not be recognized until pulmonary embolism has occurred. The most important symptoms and signs to diagnose its presence are a positive Homans' sign, pulse rate increased out of proportion to the body temperature, an increase occasionally in circumference of the involved limb, and regional pain or tenderness.

1. Analysis of 172 Cases Treated at the Pennsylvania Hospital, 1933-1953.—In the twenty-year period of 1933-1953 there were 172 patients in whom the diagnosis of venous thrombosis of the lower extremities was made during the postpartum period at the Pennsylvania Hospital. There were 50,332 deliveries in this twenty-year period, an over-all incidence of 0.34 per cent (Fig.

4). Twelve patients gave a history of venous thrombosis in prior pregnancies. Pulmonary embolism was recognized 29 times and was the primary cause of death in 7 patients. The incidence of known pulmonary embolism thus was 16.9 per cent in the 172 patients and the death rate was 4 per cent. Of the 29 patients with known pulmonary emboli, 24 per cent died. It is only within the past several years, however, that we have become more aware of the varied manifestations of less serious pulmonary emboli, with or without infarction. Unquestionably, numerous patients had pulmonary emboli in the puerperium which were diagnosed as pneumonia, atelectasis, pleuritis, or possibly acute cardiac failure.

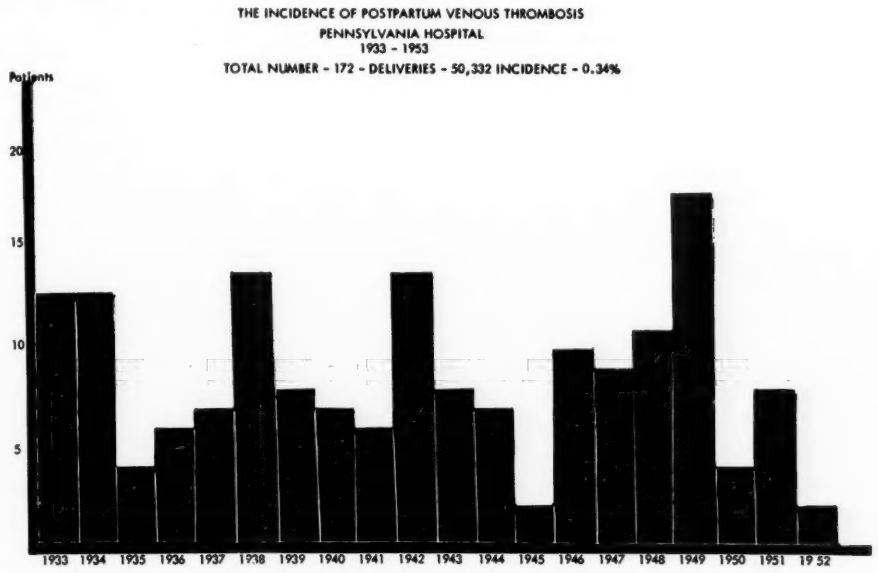

Fig. 4.—The incidence of postpartum venous thrombosis, Pennsylvania Hospital, 1933-1953.

A study of the complications or added operative interventions following delivery of 170 patients who developed venous thrombosis revealed 43 cases, or 25 per cent, with some added factor of trauma, infection, or disease which could have been contributory.

TABLE IV. THE INCIDENCE OF POSTPARTUM COMPLICATIONS DUE TO VENOUS THROMBOSIS

COMPLICATIONS	NUMBER OF CASES
Pyelitis	10
Endometritis	7
Sterilization	5
Toxemia	3
Sulcus laceration	3
Hemorrhage	3
Appendectomy	1
Psychosis	2
Wound infection	2
Pneumonia	2
Syphilis	1
Peritonitis	1
Tonsillitis	1
Rheumatic heart disease	1
Septicemia	1
Total	43

Types of Delivery Employed: The various methods used for the termination of pregnancy and delivery of the fetus in the 172 patients who developed postpartum venous thrombosis are given in Table V in order of their frequency.

TABLE V. METHODS UTILIZED FOR DELIVERY OR TERMINATION OF PREGNANCY IN 172 PATIENTS WHO DEVELOPED POSTPARTUM VENOUS THROMBOSIS

METHOD	NUMBER OF CASES
Low forceps	68
Cesarean section	51
Spontaneous	35
Breech extraction	6
Version	5
Midforceps	4
Spontaneous breech	3
Total	172

Table V shows that 51 (or 30 per cent) of our 172 patients with postpartum venous thrombosis were delivered by cesarean section. This figure leaves little doubt as to the increased hazard of venous thrombosis following abdominal delivery. Difficult operative procedures as breech extraction, version, and midforceps delivery also increase the factor of trauma and the predisposing cause of venous thrombosis.

Anesthesia: The types and frequency of anesthesia used in this series are listed in Table VI. Ether, or nitrous oxide and ether, were most often used in patients admitted to the hospital before 1940. More recently, spinal, continuous caudal, and nitrous oxide have been in general use. As the employment of these methods was not strictly controlled, no conclusions can be drawn regarding the superiority of any one of these methods in preventing venous thrombosis of the lower extremities. It is our impression, however, that regional or local analgesia may aid in lowering the incidence of thrombosis by their action of peripheral dilation of the circulatory system of the legs and thus decreasing the spasticity of the vessels.

Table VI reveals that 50 patients (or 30 per cent) had regional analgesia for delivery, and 122 patients (or 70 per cent) received general anesthetics. Since approximately 80 per cent of our patients delivered in the hospital have regional analgesia, it is seen that the relative incidence of venous thrombosis is lower in this group.

TABLE VI. TYPES OF ANESTHESIA UTILIZED IN THE DELIVERY OF 172 PATIENTS WHO DEVELOPED POSTPARTUM VENOUS THROMBOSIS

ANESTHESIA	NUMBER OF CASES
Ether with nitrous oxide	62
Ether	15
Spinal	37
Nitrous oxide	25
No anesthesia	17
Continuous caudal	11
Local (pudendal)	2
Cyclopropane	1
Chloroform	1
Pentothal and ether	1
Total	172

Ambulation: Opinions differ in the various studies which attempt to evaluate the physiological effect of early ambulation and leg exercises in the

prevention of venous thrombosis in surgical cases. Little has been written concerning this problem as it refers to the postpartum patient.

In the early years of this study of thrombosis in postpartum patients (1933-1940) the usual practice was to keep patients who were delivered vaginally in bed for ten to twelve days in the semi-Fowler or absolutely flat position. Those who had cesarean sections were kept in bed in these positions even longer, 12 to 15 days. Little attention was given to leg exercises during this time.

Gradually (1940-1946) earlier rising from bed was practiced—eight to ten days for the normal postpartum patient and some increased attention was given to leg exercises. During 1947 ambulation for patients delivered vaginally was started two to three days post partum and seven days post partum for the cesarean section patients. This was continued and the time was gradually reduced during the next two years (1948-1949), but early ambulation was irregularly practiced by the staff obstetricians.

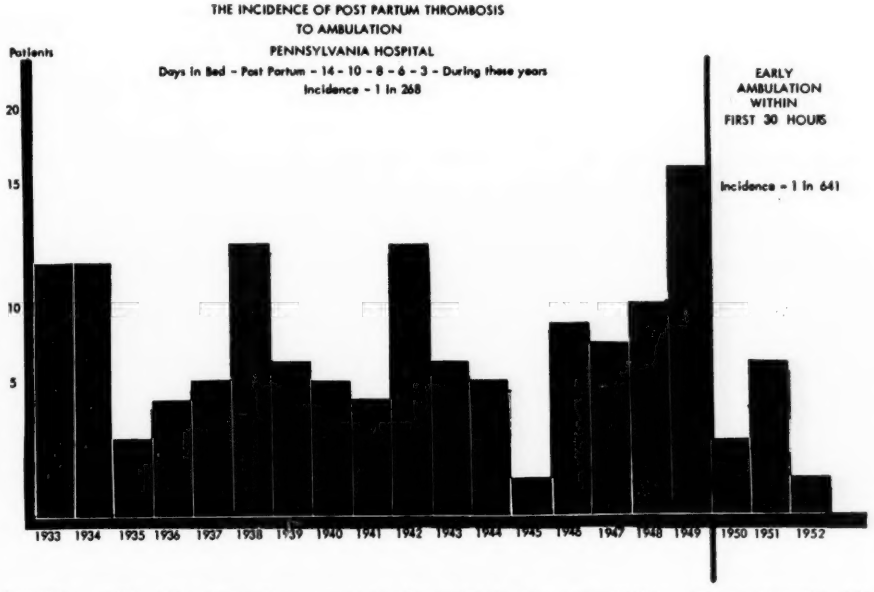

Fig. 5.—The ratio of postpartum venous thrombosis to ambulation, Pennsylvania Hospital, 1933-1953.

It was not until 1950 that early, more energetic ambulation of all postpartum patients was made the rule of the hospital and practiced on each patient unless some serious postpartum complication such as eclampsia or hemorrhage prevented. As a result, for the past three years almost all delivered patients have been encouraged to get out of bed within the first 24 hours or shortly thereafter.

In the analysis of the 172 patients with postpartum venous thrombosis, the average time for the onset of venous thrombosis in all patients was 7.6 days. For patients who were delivered by the vaginal route, it was 6.3 days, and for patients with cesarean section, 10.4 days. Thus, except for the last three years (1950-1953) the disease developed while the patients, for the most part, were confined to bed.

The relation of postpartum venous thrombosis to early ambulation is seen in Fig. 5. In the three years, 1950-1953, that early ambulation has been practiced, there were 14 patients in 8,983 who developed venous thrombosis, or an

incidence of 1 in 641. This is contrasted with the preceding 17 years of this study, 1933-1950, in which 158 patients in 41,349 developed thrombosis, an incidence of 1 in 268.

Although we have practiced early ambulation as a standardized regimen for only three years, and much more time must elapse before definite conclusions can be drawn, we feel that this procedure has great merit and may possibly diminish the incidence of postpartum venous thrombosis.

In order to accomplish this regimen, it is the obstetrician's responsibility to order the time, frequency, and amount of ambulation and leg exercises that are to be carried out by the patient. It is the obstetrician's responsibility also to see that the nursing staff is specifically instructed and that no laxity occurs. He should advise that the patients get out of bed at the earliest possible time after recovery from anesthesia, and at regular, frequent intervals thereafter.

Telling the patient of its value will greatly facilitate early ambulation. Offering calm, convincing reassurance that early rising from the puerperal bed and exercising the legs will do much to lessen the likelihood of blood clots in the veins of the legs will add much to the patient's confidence and desire to cooperate.

Treatment of Postpartum Thrombosis: The treatment prescribed for venous thrombosis for the 172 patients under our care is seen in Table VII. By "conservative" treatment is meant the use of heat, elevation, ice, or plastic bandages and sedatives. It is without anticoagulants or surgery. Conservative treatment was the usual method prior to anticoagulant therapy.

TABLE VII. TREATMENT PRESCRIBED IN THE CARE OF 172 PATIENTS WHO DEVELOPED POSTPARTUM VENOUS THROMBOSIS, AND ITS RELATION TO PULMONARY EMBOLI AND DEATH

TREATMENT	NUMBER OF CASES	DEVELOPED PULMONARY EMBOLI	FATAL
"Conservative"	112	21	7
Anticoagulants	46	8*	0
Surgical ligation of veins	8	0	0
Sympathetic nerve block	6	0	0
Total	172	29 (16.9%)	7 (4%)

*Before treatment.

The 7 deaths that occurred were in the conservatively treated group—those who did not receive anticoagulants or vein ligation. There were no deaths in the group who received anticoagulant therapy, although 8 of these patients had pulmonary emboli after delivery prior to the administration of anticoagulants. The patients on whom venous ligations were performed did not develop pulmonary embolism, showing that ligation was done at the proper level or above the thrombosis.

2. Methods of Treatment.—

The treatment of postpartum venous thrombosis consists of: (a) prophylactic treatment, and (b) active treatment.

A. Prophylactic treatment:

1. Treatment of varicosities during pregnancy by injection, surgery, or elastic stockings.
2. Prevention of abnormal weight gain in the antenatal period.
3. Avoidance of infections whenever possible and prompt and adequate treatment when acquired.
4. Mature obstetrical judgment at delivery and elimination of operative and traumatic factors whenever possible.

5. Prevention of venous stasis in lower extremities during postpartum period by: (a) early, energetic ambulation; (b) avoidance of tight abdominal binders and dressings; (c) prevention of hemoconcentration from dehydration in cases of vomiting, diarrhea, fevers, prolonged labors; intravenous administration of glucose or saline solutions to maintain normal protein and hydration; (d) avoidance of chilling.

6. The use of anticoagulants in patients who had venous thrombosis in prior pregnancies. During this twenty-year period (1933-1953) 37 of our patients who had had thromboembolic disease in previous pregnancies received anticoagulant therapy. Under close regulation of clinical and laboratory studies, only one developed postpartum hemorrhage. This occurred in a patient in whom a portion of the placenta had been retained following delivery. Dilatation and evacuation of the uterus were performed without further hemorrhage.

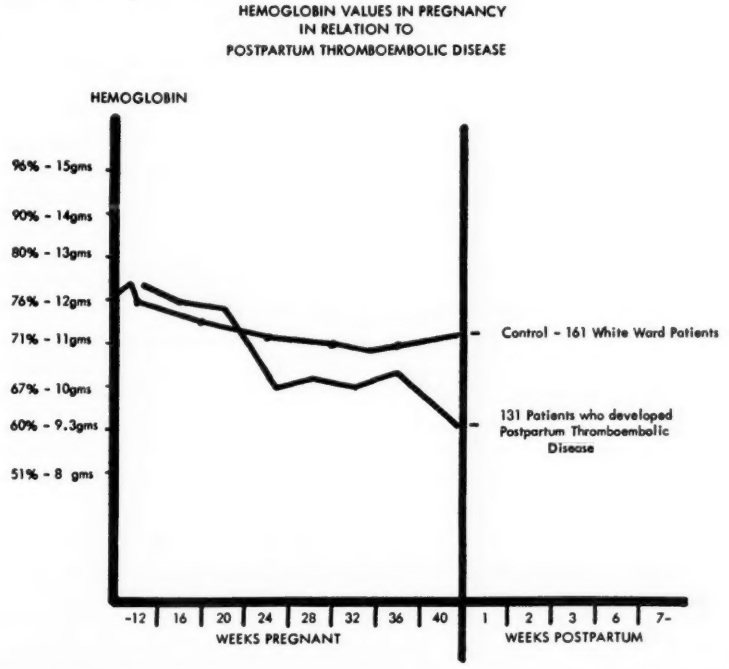

Fig. 6.—The relationship of anemia in pregnancy to postpartum thromboembolic disease.

7. Correction of anemia, by transfusion, if necessary. The correction of anemia as a prophylactic measure against thrombosis should receive special emphasis. Many physicians are aware that the incidence of venous thrombosis and pulmonary embolism is higher in anemic patients, but anemia has not been stressed as an important etiological factor. Shaw in 1924, while discussing a paper on pulmonary embolism presented by Glynn, called attention to the importance of anemia following hemorrhage as an important cause of thromboembolism, and Donald, at the same time, confirmed this view by citing additional data. In 1948, Hirschboeck again emphasized anemia as a cause of increased clot retraction and a factor in venous thrombosis. In support of this belief, Quick, in 1951, noted that massive pulmonary embolism is very uncommon or absent in polycythemia, although thromboses occur frequently. This can readily be explained by the poor clot retraction of such blood.

In this study of postpartum venous thrombosis, 132 patients had a sufficient number of determinations of hemoglobin and red blood cell count in pregnancy

to be of value in following their blood picture antenatally (Fig. 6). This is shown in relation to average hemoglobin values observed during pregnancy in 161 white ward patients at the Pennsylvania Hospital in a study by Weihl in 1950. The hemoglobin determinations made on these patients just prior to labor and delivery showed the average value to be 72 per cent or 11.2 Gm., whereas in the 132 patients who developed venous thrombosis in the puerperium, the hemoglobin value was 61 per cent, or 9.4 Gm. While no definite conclusions can be drawn from these values, they tend to support the belief mentioned that anemia is an important factor in pregnancy in the development of postpartum thromboembolic disease.

B. Active treatment: The so-called "conservative" therapy no longer has a place alone in the treatment of postpartum venous thrombosis, once the disease has been diagnosed. Certain measures, such as elevation of the affected extremity, heat, or elastic bandages may be used, but only in conjunction with anticoagulants or surgery.

1. Anticoagulant therapy should be the treatment of choice unless some contraindication exists. These contraindications include hemophilia, thrombocytopenic purpura, leukemia, open wounds or ulcerations, particularly of the gastrointestinal tract, impaired hepatic or renal function, severe hypertension, and subacute bacterial endocarditis. Anticoagulant therapy has largely replaced ligation as the active therapy in our patients. Heparin, given by the intermittent intravenous method, and/or Dicumarol by mouth have been the safest drugs in our hands. Rigid attention to controls and daily prothrombin determinations are essential if the drugs are to be used safely. It is desirable in most cases to give 50 mg. of heparin intravenously and to begin Dicumarol therapy at the same time. Three hundred milligrams is given orally, and this dosage is repeated in twenty-four hours. A *daily* prothrombin time determination is then used to control the Dicumarol therapy. In the postpartum patient it is usually safe to keep the prothrombin time close to 20 per cent of normal. Rapid subsidence of symptoms and signs has been the rule in our patients and usually they can be ambulatory in a few days. It is desirable to continue this therapy until they are quite active, usually ten to fourteen days.

2. Surgical ligation. Our experience with ligation of the veins has been limited to 8 cases. This is a natural result of the gratifying experiences with anticoagulants. It is well to remember that the only purpose of ligation of veins is to prevent pulmonary embolism. The ligation will prevent embolism only from that region which is distal to the ligature. Instances have been recorded of emboli originating from a region proximal to the ligature of one vein, or from a venous thrombosis which develops in the other leg later.

In contrast, anticoagulants are used for two purposes: to prevent pulmonary emboli from originating anywhere in the body, and to prevent extension of venous thrombosis. While it is impressive to prevent pulmonary embolism, the importance also of preventing occurrence or extension of venous thrombosis must be stressed. Anticoagulants also lessen venous insufficiency by preventing extension of the thrombosis, whereas ligation does not.

We recognize a role for ligation of veins, which at times becomes quite important. Cases of puerperal sepsis, or septic abortion, with multiple septic emboli, are best treated by iliac or vena cava ligation. In the type of cases considered in this presentation, however, we believe anticoagulant therapy is superior.

3. Lumbar sympathetic nerve block.

4. Continuous caudal analgesia.

5. Intravenous procaine.

The last three may be utilized in acute cases of thrombophlebitis with severe pain and swelling (vasospasm).

Summary

Thromboembolic disease complicating pregnancy and the puerperium occupies a prominent place in obstetrics as a disabling or fatal condition.

A total of 50,332 pregnant women were registered antenatally and delivered at the Pennsylvania Hospital from 1933 to 1953, inclusive. Antepartum venous thrombosis occurred in 9 patients (0.018 per cent). One hundred thirty-five cases from the literature are reviewed, with the results of therapy. From this study evidence is accumulating that patients who develop venous thrombosis during pregnancy are best treated by anticoagulant therapy, provided meticulous control of the prothrombin time is maintained. Owing to the rarity of the condition it is difficult to be dogmatic as to treatment. It would be of great value if all cases were reported, as in this way a more accurate idea of the frequency of occurrence, mortality rate, and results of treatment could be ascertained.

During the same period (1933-1953) 172 patients developed venous thrombosis in the puerperium (0.34 per cent). Seven patients died as a result of this disease (4 per cent). Possible predisposing factors are discussed and the results of treatment are tabulated in relation to development of pulmonary embolism and fatal outcome.

The prevention of postpartum thromboembolic disease lies in better antenatal care, mature obstetrical judgment at delivery, and the avoidance of venous stasis. Early ambulation and treatment of infections are discussed. In our experience the prevention of fatalities of this disease, once it has occurred, is best accomplished by the use of anticoagulant therapy. Close cooperation between the cardiologist-internist, the vascular surgeon, and the obstetrician is essential for successful treatment.

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Discussion

DR. CONRAD G. COLLINS, New Orleans, La.—In a four-year period from 1949 to 1952, the Tulane University service had 16,000 deliveries, in which there were 20 deaths, an average of 1.23 deaths per 1,000. We are not proud of that, but it is better than it used to be. What caused these deaths?

Embolism 7, hemorrhage 5, anesthesia 1, self-administered poison 1, sickle-cell crisis 1, pancreatitis 1, ruptured uterus with peritonitis on admission 1, toxemia 3.

So you see that 35 per cent of these maternal deaths were due to embolism. And embolism was due to: amniotic fluid embolism 3, air embolism 1, phlebothrombosis 2, tuberculosis and thrombophlebitis 1.

We mention this because in obstetrics and gynecology we have the most fertile field for embolism. Why do we mention air and why do we mention amniotic fluid embolism? Five years ago a report came from the Pathology Department of Charity Hospital that they had seen no amniotic fluid emboli. Yet in the following four years by careful search for the condition we found 3 such cases. Deaths in obstetrics are usually ascribed to pulmonary embolus, so unless one obtains a postmortem and looks carefully for the material from the amniotic fluid embolism, the diagnosis is missed. If an autopsy is not granted then blood should be aspirated from the heart, centrifuged, and a smear made from a layer between the red blood cells and serum. If amniotic fluid embolism has occurred, squamae and lanugo hair will be observed. Also cases of air embolism will be documented in this manner, as in air embolism frothy blood and/or air will be aspirated from the heart.

I do not agree with Dr. Ullery that anticoagulants are superior in most instances to vein ligation. I think the point he made this morning is that if we look for phlebothrombosis and if it is found and treated in a modern way by anticoagulants or ligation or a combination of both, we will prevent a lot of deaths due to pulmonary embolism from blood clot.

As you can see, in this four-year period embolism of one kind or another accounted for 35 per cent of the deaths, and we want to say that we think prophylaxis begins with the history. There is in Dr. Ullery's group a high incidence of patients with previous embolic episodes. All obstetric and gynecologic histories should have the information of previous vascular complications of any sort because those are the people who are more prone to have a recurrence. We do not use prophylactic vein ligation or anticoagulants except in pregnant women with a history of previous embolic episodes. When such a patient goes into labor, she is given anticoagulants.

Dr. Ullery has called to our attention that anticoagulants are safe to give during the period of gestation and in his cases no hemorrhage occurred.

In conclusion, we still pay attention to varicose veins and have them treated during pregnancy. We use lumbar block and ligation and occasionally anticoagulants, but we also use early ambulation. In the most severe cases where we get massive occlusion of the veins of the extremities with gangrene, "phlegmasia cerula dolens," the only thing that seems to be of benefit—whether we use block, anticoagulants, or ligation—is early flexion of the foot on the leg, flexion of the leg on the thigh, and the thigh on the abdomen, a pumping motion. It is necessary to have patients who are confined to bed move their legs every day, many times.

DR. WILLIAM E. STUDDIFORD, New York, N. Y.—Dr. Ullery mentioned in his review of the literature a case reported by Drs. Sachs and Labate in 1949 from the obstetrical and gynecological service of Bellevue Hospital. This represents one of the earliest cases of antepartum thrombophlebitis and pulmonary embolism treated with anticoagulants. Dicumarol was the drug used. The patient did very well but during the course of treatment the fetus died in utero. Some time after its death, normal delivery took place. Autopsy of the fetus revealed that, in spite of the macerated condition, quite extensive hemorrhages occurred in the mediastinum and subperitoneal tissues. Since then we have treated several cases of antepartum thrombophlebitis with anticoagulants but have not noted any accidents such as this. I would like to know if Dr. Ullery discovered any particularly high incidence of intrauterine death in the cases he reviewed.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—This subject is important to everyone and especially to obstetricians. Prior to Jan. 1, 1947, all obstetrical patients remained in bed for eight days, were permitted up on the ninth day, and discharged on the tenth day or later. On Jan. 1, 1947, we instituted early ambulation, meaning that the patients

could get out of bed within 24 hours after delivery if they so desired. They were not to go to the bathroom until the second day and outside of the room on the fourth day. Shower baths were not permitted until the fifth postpartum day. Various observations have been made both before and since this practice was instituted and we hope to report these within the year. We are especially interested in trying to decrease maternal deaths due to pulmonary embolism which is becoming an important cause of maternal deaths since the total number of such deaths from other causes has steadily decreased. In the period from May, 1931, to Dec. 31, 1946, there were 46,877 deliveries. There were 4 deaths due to pulmonary embolism proved by autopsy and a fifth in a cardiac patient whose clinical course supported the diagnosis. This gives an incidence of pulmonary embolism of 0.011 per cent. In the period from Jan. 1, 1947, to Dec. 31, 1953, there were 27,098 deliveries and 4 deaths proved to be due to pulmonary embolism, an incidence of 0.015 per cent. Obviously, early ambulation has not decreased the incidence of fatal pulmonary embolism when one considers the marked reductions in maternal deaths from other causes. It is disappointing that deaths from embolism not only still occur but are actually comprising a higher percentage of the total number of maternal deaths. It is of interest that in the first series two of the deaths were after cesarean section and in the latter series three of the deaths were after cesarean section.

Early ambulation has resulted in a clinical test which we would not have permitted had we been cognizant of it. Patients would develop pain in the leg or thigh and frequently wait two or more days before mentioning it. On examination there was obvious thrombosis. Initially, we placed these patients at bed rest but as we appreciated the clinical experiment, we have not restricted these patients and have permitted them to go home at a much earlier date than we originally did.

Anticoagulant therapy has been used in some of our patients but we have not been satisfied with the result. I cannot state that any patient actually died from this therapy but we have had some anxious moments while trying to control hemorrhage from the postpartum uterus and to replace the tremendous blood loss. We have also been concerned about the possibility of renal damage from the hemorrhage. In the majority of our cases where anticoagulant therapy was instituted, it was done primarily at the insistence of one of our medical or surgical colleagues who thought it would be a preventive procedure.

DR. JOHN C. ULLERY, Philadelphia, Pa. (Closing) (By invitation).—In answer to Dr. Studdiford's question concerning fetal deaths in antepartum patients with thromboembolic disease, so far as I could tell in the review of the literature, Dr. Sachs' was the only such case. As I recall in going over that report, the patient received an enormous amount of Dicumarol. It was difficult to control the pulmonary emboli prior to her delivery. She received much more of the drug over that period of time than any other patient of whom I have a record. Whether that was a factor I do not know.

As for Dr. Dieckmann's questions, we do not believe that early ambulation is the only preventive factor in this condition, but we do feel it may play an important role. Active leg exercises are important, too. Thirty-seven of our patients received prophylactic anticoagulant therapy after delivery and in this group there was no postdelivery hemorrhage except in one patient from whom there was excessive bleeding on the fourth day. Dilatation and evacuation revealed a portion of retained placenta, and with its removal there was no further bleeding. I have had no other experiences of hemorrhage in postpartum thromboembolic disease.

THE DISTRIBUTION AND FUNCTIONAL ACTIVITY OF THE CERVICAL MUSCULATURE*

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IN 1947, I presented a paper[1] which demonstrated that the human cervix is composed predominantly of fibrous connective tissue. This finding was promptly confirmed in this country.[2] Recently, however, two British workers have pointedly challenged this thesis, and state that the findings are misleading,[3] that they "suggest entirely false inferences,"[3] and that I was misled by an artifact which resulted in an entirely erroneous concept of the structure and function of the uterovaginal canal.[4] A recent article[5] ignores the 1947 work and implies that it represents an archaic line of thought. In addition, a third British observer[6] in February of this year has commented that I failed to recognize a muscle pattern in the cervix simply because the methods of examination were inadequate for this purpose.

These latter statements represent the most recent information upon this subject. In my opinion, however, they may not be considered as final for the reasons that certain of the conclusions are entirely without basis, and all of the materials and techniques are not wholly consistent with standard and proper procedure. Accordingly, a further evaluation of this matter is mandatory. This evaluation, which may be considered a rejoinder, should properly (I) summarize the pertinent aspects of the 1947 paper to serve as a convenient point of departure; (II) examine and evaluate the work which denies my original findings; and (III) make such additions to the original material as may be necessary to answer these questions with finality. Such are the purposes of this paper.

I. Summary of Original (1947) Work

The material consisted of 12 pregnant and 46 nonpregnant uteri obtained by complete hysterectomy. The specimens were either opened and sectioned immediately after their removal, or were promptly injected with Bouin's solution in order that instant fixation might be obtained. Large blocks of the cervix and isthmic segment were prepared, sectioned at 6 to 10 microns thickness, and stained with Masson, Milligan, or van Gieson trichrome techniques. These stains provide a sharp color contrast between muscle fibers and the collagen fibers which are the basic constituent of fibrous tissue. *In such preparations, it was possible to delineate a level which was referred to as the fibromuscular junction, below which the tissue was predominantly fibrous, and*

*Presented by invitation at the Seventy-seventh Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 20, 21, and 22, 1954.

above which it was essentially muscular. This level corresponded approximately to the histological internal os of Aschoff, and was considered to demarcate, for functional purposes, the upper extremity of the cervix. It is pertinent here to quote directly the passages from that paper in which the structure of the cervix was ultimately defined. By the use of differential stains for fibrous tissue and smooth muscle, "The basic structure of the cervix is found to be fibrous connective tissue. In many specimens virtually no smooth muscle can be found. From this extreme one passes to other specimens in which moderate amounts of muscle are present; occasionally this may reach as much as 40 or 45 per cent although ordinarily it does not exceed 10 or 15 per cent. When muscle does appear in cervical sections, its distribution shows great variability. Ordinarily the muscle fibers are scattered at random throughout the substance of the cervix. Rarely they appear in small bundles near the central portion of the tissue, being either isolated or continuous with the muscle tissue superior to the cervix. The inconstancy of such central bundles and their attenuate appearance when they are present make it unlikely that sphincteric possibilities could be attributed to them."

II. Summary and Evaluation of Recent British Publications

1. W. C. W. Nixon.—The portion of Nixon's work which he relates to the foregoing findings has to do with cervical contractility. Employing intrauterine and intracervical balloons, he presents a series of kymographic tracings which purport to demonstrate that the cervix is capable of independent contractility. He presents no original information concerning cervical structure, but relates at length the findings of Hughesdon which are reviewed hereafter.

In his first paper, the statement appears that "from Danforth's study it would appear that the cervix consists mainly of fibrous tissue. If this view is accepted it would be difficult to reconcile it with the records just presented which indicate that the cervix of the pregnant human uterus has an independent contractility." In the second article the following appears: "It has long been held that the cervix is composed essentially of fibrous tissue. If this were so then the above records of cervical activity could not have been obtained in the complete absence of muscle contractility." The closing statements of both of these quotations are fine examples of the non sequitur, since the conclusions are entirely illogical. My statement that the cervix is composed predominantly of fibrous connective tissue by no slightest implication entitles one to conclude that no muscular activity could ever be demonstrated. For reasons which are equally nonapparent, the 1947 work is described later as "suggesting the entirely false inferences that the cervix cannot contract and relax, and that its behavior can never be influenced by drugs." It is of passing interest that Nixon now adds, "Possibly this is so, but the reason is not anatomical." This observation indicates some doubt concerning his own findings and suggests the possibility that the contractions which he records are either transmitted from the corpus, or are otherwise extracervical.

To summarize: Although Nixon's tracings are not wholly convincing, nevertheless his finding that the cervix can contract agrees with prior work and is in no way incompatible with my own structural findings.

2. P. E. Hughesdon.—Hughesdon's work was "prompted by the recent reopening of the subject of cervical structure by Danforth (1947) and others." His findings were recorded in preliminary fashion in 1949,[7] reviewed in detail by Nixon in 1950,[3] and formally presented in 1952.[4]

His material consisted of 57 uteri, of which 14 were pregnant. Twenty-five specimens were obtained by complete hysterectomy, 6 by Wertheim hysterectomy, and 26 by autopsy. In addition, median sagittal slices, evidently of the cervix and isthmic segment, were obtained in 6 cases at the time of hysterotomy and sterilization.

On the basis of this material, Hughesdon concludes that the cervix consists of an outer fourth which is mainly muscular, and an inner three-fourths which is mainly collagenous. The outer layer is found to form a complete "investment" of the cervix, and to be continuous with the corporeal muscle above and the vaginal muscle below. This muscle was thought to be significant in amount and to have functional importance.

Hughesdon considers my original data to be in error through artifact. It is his contention that since all of my material was obtained by hysterectomy, (a) the outer muscle layer is frayed by the pulling out of connective tissue fibers during dissection of the bladder, and (b) the outer layer is obscured by postvital retraction. Also, at this point, mention is made by Hughesdon that the outer muscle layers being relatively loose are readily penetrated by fixative and stain well, whereas the inner layers are more dense, and are likely to fix and stain poorly. He observes that this latter defect is "encountered in all material" but especially so in autopsy material, "where there is always some autolysis."

In evaluating Hughesdon's work, commentary should be made concerning the following:

1. It is generally accepted that contrast stains of the Masson or Mallory type when properly used enable one to differentiate between fibrous tissues and smooth muscle. But it is, or should be, elementary that accurate histological work of any type requires proper fixation of tissue.[8] This is pointedly emphasized by Bartelmez.[9] Such a requirement appears to be particularly necessary when the work of a contemporary student is described in the terms which Hughesdon has employed. In his material, two specimens selected for illustration were obtained, respectively, in 1899 and 1903. Fixation and subsequent differential staining were probably something less than ideal in these specimens which evidently reposed in a museum for approximately half a century. Dates are not given for most of the remaining specimens, but many are presumed to be modern. In two of these, also selected to illustrate the differentiation of muscle and fibrous tissue, specific mention is made of the obscuring of details by poor fixation.

No details of fixation are given except that the material was fixed in 10 per cent formol saline. In one case it is specifically stated that the entire uterus was "removed and fixed unopened." In such a case complete penetration by fixative would be expected to require between 24 and 48 hours, thus allowing a considerable time for autolysis in the deeper layers. This needs no further comment, since Hughesdon himself has already emphasized the fallacy of attempting to interpret tissues such as this with finality.

2. Concerning Hughesdon's objections to hysterectomy material, it is inconceivable to me that surgical separation of the bladder from the anterior aspect of the cervix by following the easy plane of cleavage through the loose areolar tissues separating these structures could possibly be thought to remove the outer fourth of the cervix. Similarly, the amputation of the posterior vaginal vault could hardly leave one-fourth of the thickness of the cervical wall in place. A telling inconsistency of Hughesdon's argument appears in one of his figures (No. 7). This is a photomicrograph which illustrates his so-called extrinsic muscle layer, the layer which is said to be absent in hysterectomy material. The specimen for this illustration was obtained by removing a slice from the uterus at hysterotomy and sterilization. Hence, the layer, if present, does not require autopsy or Wertheim material for its demonstration, as he insists elsewhere in the article.

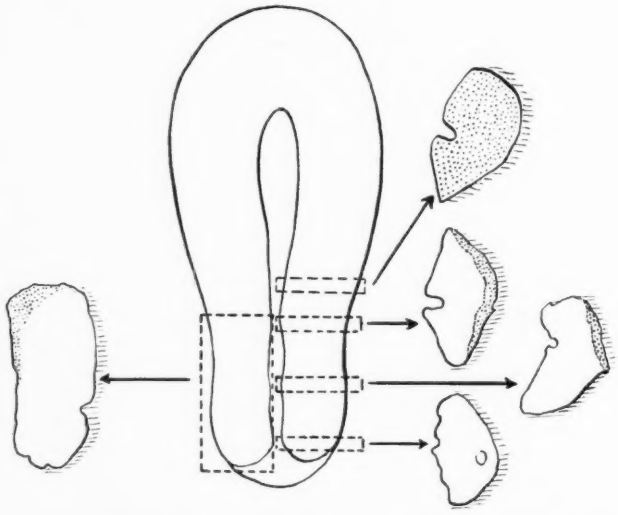

Fig. 1.—Diagram to indicate tissues removed. Stippled area shows portions which are predominantly smooth muscle; clear areas of cervix are predominantly fibrous. Section on left is longitudinal, those on right are transverse, being taken at (1) the level of the external os, (2) the mid-portion of the cervix, and (3) the upper cervix just below the anatomical internal os. A fourth section, as control, is removed from the corpus just superior to the anatomical internal os.

III. Additional Data

At the outset, it appears necessary to state our conception that the operation which we term "total" or "complete hysterectomy" results in the removal of the entire uterus, and that any contiguous or adjacent or connected tissues which are not removed by this operation cannot properly be con-

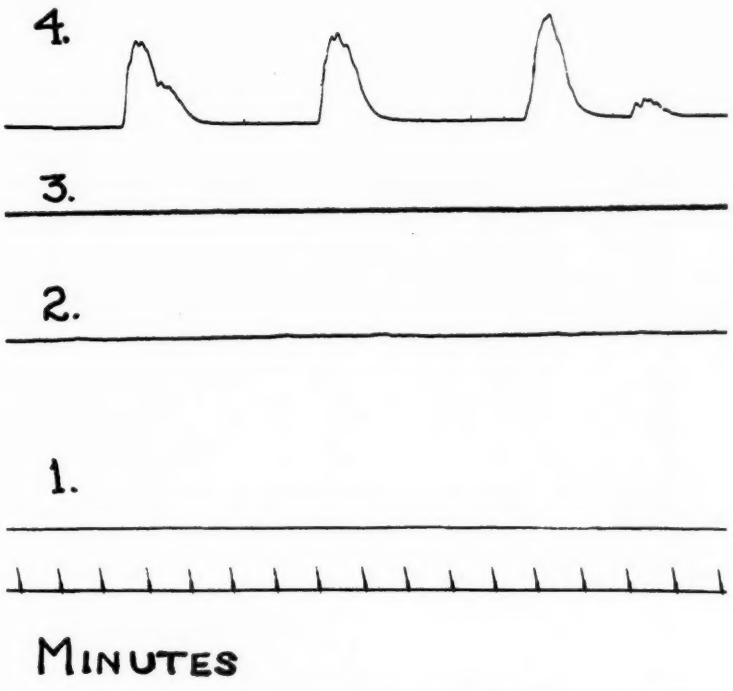

Fig. 2.—See text. Nonpregnant uterus. Strip *1*, level of external os; *2*, midcervix; *3*, upper cervix; *4*, corpus control.

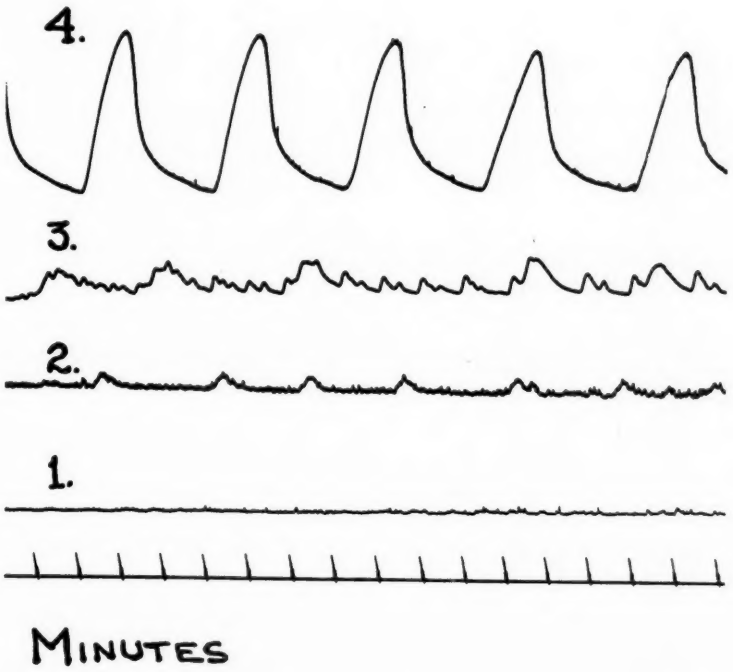

Fig. 3.—See text. Pregnant uterus. Strips same level as indicated for Fig. 2. Contractions shown are response to Pitocin 0.1 unit per 100 c.c.

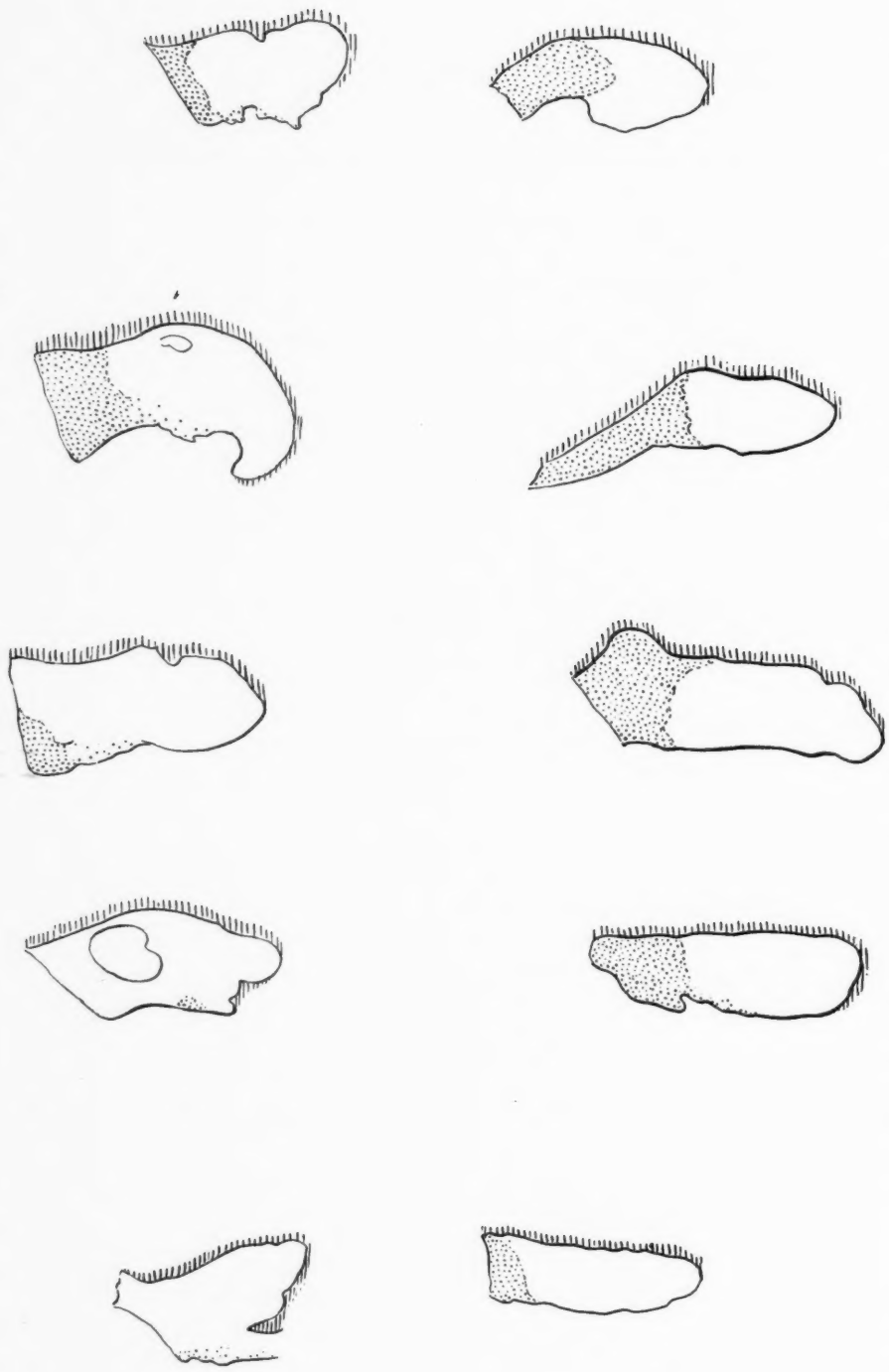

Fig. 4.—Tracings of representative longitudinal sections to show fibromuscular junction. Upper specimens pregnant, lower nonpregnant. Endocervix to right in all sections except lower middle, which is to left. Stippled area predominantly smooth muscle, clear area predominantly fibrous. Fibromuscular junction in all cases conforms approximately to level of histological internal os.

sidered to be a part of the uterus. Accordingly, it follows that if one wishes to study the structure of the human uterus, he may turn with confidence to the tissues obtained by complete hysterectomy.

Two questions which now require answers are: (1) Is the human cervix, as now defined, capable of independent contractility, and (2) is there a consistent distribution pattern of smooth muscle in the human cervix?

1. The literature concerning cervical contractility has been well reviewed[10] and need not be repeated here. Because of the conclusions of both Nixon and Hughesdon, however, it seemed desirable to test cervical motility in the excised uterus. An obvious and accurate test of the ability of the cervix to contract and relax is to suspend excised strips in an appropriate bath and to record any activity. Accordingly, this was done in 10 cases. All of the women were between the ages of 30 and 42 except for one, aged 47, who was approximately two months pregnant. In 7 of the remaining 9 cases the endometrium was found to be in the proliferative phase, and in 2, the secretory phase. The cervices were sectioned immediately after removal at approximately the levels indicated in Fig. 1. In addition, a fourth strip was removed from the corpus immediately above the anatomical internal os to serve as a control. The strips were cut from the flat surface of the transverse section, and were approximately uniform in size (18 by 4 by 4 mm.). The trimmed strips were placed in chilled Tyrode's solution and immediately transported to the laboratory. They were then suspended in oxygenated Tyrode's solution at 37° C.; strips *1* and *2*, and strips *3* and *4*, were placed together in each of two separate baths. Each strip was connected to a writing lever with 1:6 fulcrum and 1 Gm. weight. Tracings of the four strips from each uterus were made simultaneously.* In all of the 10 specimens, characteristic spontaneous activity and reactivity were recorded in the corporeal strip, labeled *4* in Figs. 2 and 3, within fifteen minutes. In the nonpregnant cases no activity or reactivity was observed in any of the three cervical segments, irrespective of stimulation by high concentrations of Pitocin and histamine, altering the fulcrum ratio, or waiting up to three hours' time. In the pregnant case, although no spontaneous cervical activity occurred, the addition of Pitocin to the baths in a dose of 0.1 unit per 100 c.c. induced the contractions shown in Fig. 3.

2. In order to determine the distribution of the smooth muscle within the cervix, the material from the previous study was re-evaluated and, in addition, 48 new specimens were obtained. Of the 104 uteri which were studied, all were obtained by complete hysterectomy. In many, a cuff of vaginal vault was present. Six autopsy specimens were obtained, and were found to add no new information. In 42 cases the slides were prepared by recutting from blocks which had been processed in the manner which is routine for surgical specimens, namely, cutting the fresh tissue within two or three hours of its removal and fixing immediately. In the remainder, which were prepared especially for these studies, the specimens were obtained immediately upon removal. Whenever it was desired to retain the original shape of the specimen for accurate sectioning, the thickness of the wall throughout its length was injected with fixative and sectioning was deferred until fixation was sufficient to allow sectioning without distortion. In the others, the uterus was opened immediately and thin slices of fresh tissue were cut and fixed. In all cases, median sagittal strips were taken, usually of both anterior and posterior walls. In 29 cases transverse sections were taken at the various levels, as indicated in Fig. 1.

*These procedures were carried out through the cooperation of Dr. W. E. Hamburger of G. D. Searle & Company.

The differential stain most commonly employed was the Milligan[11] stain. Less frequently the modified Masson, or van Gieson techniques were used.

In the specimens which we have examined, employing the techniques for sectioning, fixation, and staining which are outlined here, the cervix was found to be fundamentally a fibrous-tissue structure.

The fibromuscular junction, as previously noted, was irregular, wavy, and located at about the level of the histological internal os. The junction of muscle and fibrous tissue was sometimes abrupt, sometimes very gradual, occurring over the course of 5 to 10 mm. The substance of the cervix was again found to be marked irregularly by the presence of strands of muscle, which were extremely attenuate, and which occurred in variable amounts in the different cervices. Although Hughesdon considers it "pointless to try to put an exact figure to the proportion of muscle as judged by a general impression," the careful observer by simply looking at the slides necessarily obtains an over-all conception as to the preponderance or relative lack of a given type of tissue. Accordingly, the considered judgment given now is in accord with that made previously in good conscience, to the effect that in most complete hysterectomy specimens the average total amount of smooth muscle in the human cervix approximates 10 or 15 per cent; in the occasional case the smooth muscle content may be as high as 40 or 45 per cent. Occasionally there is virtually no smooth muscle to be found. Hughesdon's "distinct submucous layer in which the muscle content is unusually high" was evident with no consistency whatever, and was an exceptional finding.

No consistent distribution pattern of cervical muscle could be found except in the fringe or most peripheral areas of the portio supravaginalis where rather uniformly there appeared moderate to heavy strands of smooth muscle, the bundles of which ran in all directions and were separated from one another by considerable amounts of collagen. These strands were better developed laterally, about the uterine vessels, than either anteriorly or posteriorly. They were virtually absent from the portio vaginalis. In the specimens in which the vaginal vault was attached, the muscle continued into the vagina, as Hughesdon found, and was also continuous with the corporeal musculature above. *Despite this continuity, the thin, scattered, attenuate muscle strands embedded in this heavy collagen matrix were entirely dissimilar from the powerful, closely packed, collagen-sparse corporeal musculature.*

Comment

In this study, the differentiation of fibrous tissue from smooth muscle is largely dependent upon the brilliant color contrast of red and green in the Milligan and Masson stains, of red and blue in the Masson modification, and of red and orange in the van Gieson. Full color reproduction is therefore necessary for the accurate presentation of this material. Since the cost of such reproduction prohibits its use, one may choose between black and white photographs, which are striking but not especially informative, and diagrammatic sketches which outline the author's interpretations. The latter technique was considered preferable, and is employed here.

Study of the microscopic material provides full confirmation of the thesis reported in 1947, to the effect that the human cervix uteri is composed predominantly of fibrous connective tissue.

It is evident that although there is not entire agreement, there is nevertheless a center ground where Hughesdon, Nixon, and I can meet in harmony. First, we agree that the cervix is mainly a collagenous structure. Second, we agree that the cervix contains muscle tissue and that this muscle is capable of contracting. Furthermore, study of the material presented here confirms Hughesdon's findings of the presence of muscle tissue at the peripheral aspects of the cervix, which was not remarked upon before. But at this point we diverge sharply, since my conception of this muscle tissue is entirely different from Hughesdon's. As previously noted, the layer is extremely loose, is very attenuate when compared with the corporeal musculature, and in our specimens is entirely limited to the supravaginal portion of the cervix. In those of our specimens in which the vaginal vault was attached, strands of muscle are seen to continue into the vaginal vault. When the cervix was sectioned tangentially the layer appeared to be much thicker than it actually is; *when seen in precisely perpendicular section or in transverse section, the attentuate nature of this tissue is clearly evident.* As Hughesdon points out, this tissue is similar to the muscle of the vaginal vault. Accordingly, one presumes that its active contractile function is probably of the same order of importance as that of the vaginal vault which I am sure is negligible.

What, then, are the functions of this muscle tissue which is attenuate, which is haphazardly scattered through the substance of the cervix, and which tends to be slightly concentrated peripherally, and especially so at the lateral angles of the cervix? It is of course impossible to answer this question conclusively. When one considers the characteristics and distribution of this tissue, however, it is reasonable to suggest that it may serve the purpose of protection for the uterine vessels during pregnancy and labor, and also that it may be concerned in the prompt return of the cervix to its normal contours immediately after the conclusion of labor. Further conjecture is not permissible on the basis of the data at hand.

Conclusions

1. The human cervix is composed predominantly of fibrous connective tissue.

2. The so-called cervical musculature consists of isolated, attenuate strands of smooth muscle which are embedded in a heavy collagenous matrix. These strands are variable in amount in the different cervices, and are irregularly scattered except in the most peripheral areas of the portio supravaginalis, where they tend to be concentrated. They are slightly more abundant about the uterine vessels than elsewhere.

3. These strands of cervical muscle are continuous above with the muscle of the corpus, and are reflected inferiorly onto the vaginal vault. They bear

a strong resemblance to the muscle of the upper vagina; but they bear no evident similarity to the heavy, closely packed, collagen-sparse muscle bundles of the corpus.

4. The contractile ability of the cervix, as evidenced by in vitro studies, is negligible when compared with that of the corpus.

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Discussion

DR. LEROY A. CALKINS, Kansas City, Kan.—Ever since the work of Reynolds demonstrated a definite gradient of uterine contractions from the fundus downward, and especially that aberrations of this gradient might well lead to abnormal labor, the muscle content of the lower uterus and cervix has become of more than academic interest. The work of Nixon and Hughesdon, quoted by Dr. Danforth, and the even more recent work of Caldeyro of Montevideo, Uruguay, seem to indicate that the cervix possesses some degree of contractility. From purely clinical studies we have not thought this to be true. We are still not completely convinced by the experimental evidence so far available. Dr. Charles Hunter of our department is at present engaged in an extensive effort to determine whether it—the cervical contractility—is an independent activity or merely a transmission of upper uterine action to the noncontracting cervix.

Dr. Danforth's efforts to demonstrate anatomical structure, therefore, are to be commended. If his conclusions are successfully corroborated, and the little work we have done is in agreement with him, it is obvious that the small amount of muscular tissue in the cervix can have very little function as a constrictor.

DR. SAMUEL A. COSGROVE, Jersey City, N. J.—I have no capacity whatever to discuss the histology of the cervix, but I think that this presentation is important as indicating the truth—almost the axiom—which I have through the years of purely clinical observations of the cervix felt to be true, that is, that the cervix is entirely passive in its role in labor; that the cervix, except when diseased by extensive cicatrix or neoplasm, is never an impediment to the progress of labor. If that be true, then our concepts of so-called cervical dystocia and our efforts to overcome supposed cervical dystocia by surgical procedures attacking the cervix directly become meaningless and useless. It is necessary for the obstetrician to forget the cervix and concentrate on the adequacy of the adaptation of the head to the inlet in his consideration of the problem of management of delivery. If that adaptation is adequate, the cervix will respond to the pressure of the advancing head. Efforts should be made, in the event of trouble, to assess the adequacy of the accommodation of the head to the inlet rather than to pay attention to the cervix.

DR. KARL H. MARTZLOFF, Portland, Ore.—I have during the past year found it to my advantage to review carefully Dr. Danforth's work and similar publications. With that as a background I wish to present a few things he did not mention.

The current point of view still maintained by anatomists such as Rouvière, Grant, and Brash in Cunningham's *Anatomy,* is that the cervix is composed principally of smooth muscle, circularly arranged. On the other hand, Goss in his revision of Gray's *Anatomy* makes no special mention of this point, while Testut and Latarjet present both sides of the subject, concluding that it is a controversial matter. Dr. Danforth's presentation today and his publication in 1947 are most important, therefore, because he cuts right across lines which have been held by such commonly quoted authors as Stieve, Dührssen, and others. The report given by our own Fellow, the late Dr. Otto Schwarz, in 1951, supports Dr. Danforth's thesis almost verbatim.

DR. ARTHUR T. HERTIG, Boston, Mass.—I have only one minor point to make after first expressing my admiration for this combined functional-morphologic study Dr. Danforth has done. It is perfectly superb; his work would do credit to any professional morphologist.

The point Dr. Cosgrove made about there being no cervical dystocia is in the main true. I am not competent to discuss it from the clinical standpoint, but I have seen and others have seen and reported the expulsion or extrusion of the whole cervix which had failed to dilate during labor. I suppose, therefore, if you wanted to define those cases as cervical dystocia, you would be within your rights. Ultimately, of course, the baby was delivered but the cervix obstructed as long as it was able to.

FORUM: "THE URETER"

DR. RICHARD W. Te LINDE.—The ureter has assumed an increasingly important place in gynecology within the past decade owing to the great experiment—and I still think it is an experiment—which is going on with ultraradical surgery for pelvic malignancy. Whereas up to a few years ago the urologists were chiefly concerned with transplantation of the ureters, now many of us in gynecology have become concerned with it. Tonight we have with us men from four different clinics who have had some experience in this procedure. I think it would be interesting to get their points of view and then the meeting will be thrown open for questions and discussion.

THE EVOLUTION OF URETEROINTESTINAL ANASTOMOSES IN THE VINCENT MEMORIAL HOSPITAL*

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THIS is a report of the ureterointestinal anastomoses done upon patients who have had partial or complete pelvic exenteration operations in the Vincent Memorial Hospital. The text and tables show the results of the types of anastomoses used and the gradual evolution of our methods. No attempt is made to give end results as far as the treatment of the cancer is concerned.

Prior to 1948 practically all ureterointestinal anastomoses were done by the surgeons of the Urological Service, and the only methods in use were those employed by them. Their methods consisted mainly in the Coffey Type I and Type II anastomoses and now, as more radical surgery is being used by Surgical, Urological, and Gynecological Services, the Coffey type is being neglected in favor of "dunking," direct anastomoses, and bladder substitution. In 1948 the surgeons of the Gynecological Service began to operate upon cancers of the cervix in Stages III and IV and on other pelvic tumors of a similar extent. It was necessary for the gynecologists to learn the methods for anastomosing the urinary tract and the bowel. The era of pelvic exenteration, started by the fundamental work of Alexander Brunschwig of the Memorial Hospital in New York, found our group fairly ignorant of the methods and the results arising from such procedures. Up to the present time—1954—68 radical operations have been done (53 total and 15 anterior pelvic exenterations), entailing 126 anastomoses. Eight have had serious leakage and three of these have had the anastomosis redone in the same or another piece of bowel. Four others have had a kidney removed, ureter tied off, or other methods used to drain the urinary tract. One leak was found at autopsy and was not recognized during the postoperative period. Sixteen ureters developed stricture, but only 5 came to

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nephrostomy and one to nephrectomy for sepsis and stones. The remaining 102 anastomoses have appeared to function properly; 15, however, were in patients who died too early in the postoperative period for proper evaluation. Unfortunately, we do not have pyelograms on all the survivors of this radical type of surgery. Four patients, however, who successfully survived the operation have fallen by the wayside from urinary complications. There have been 50 patients with 87 anastomoses who are considered to have been in satisfactory condition. We believe that partial and complete exenteration operations depend for their success upon the proper treatment of the urinary tract almost as much as upon freedom from recurrence of the tumor. It is very evident that it is important to avoid anastomosing heavily radiated ureters and bowel. It is better to shorten the ureter and choose an area high in the descending colon for the anastomosis, rather than to chance a union between radiated structures. Inasmuch as a large percentage of cases in the exenteration group have had radiologic attempts to cure, this tissue change is important to evaluate in doing surgery upon them. Radiation therapy causes arteriosclerosis of blood vessels and an increase in scar tissue. Successful surgery demands soft, pliable structures and a good blood supply.

The Methods

The "dunking" anastomosis, or placing the end of the ureter into the lumen of the bowel through a stab wound, was the earliest method tried because it seemed simple and because it had been reported as satisfactory by Dr. Brunschwig. In this operation the ureter is cut off with a sharp knife or scissors. The end of the ureter can be opened slightly by a fish-mouth incision or cut slightly on the bias to provide a larger opening. An area in the colon is found that allows the ureter to approach it easily and permits the bowel to lie against the posterior peritoneum without tension on the ureter. A small opening is made in the bowel by means of scissors or knife, first cutting through the serosa and then through the pouting mucosa. A long, fine chronic suture is placed through the tip end of the ureter and tied. The best suture material is 00 or smaller on a long, curved, intestinal, atraumatic suture. The needle is placed into the bowel opening and goes through the mucosa and serosa about one to one and a half inches from the small opening. Then the other end of the fine catgut is threaded into another fine but long intestinal needle and is placed like the other, through the mucosa and serosa of the bowel, and exits about 1 to 2 mm. from the other strand of catgut. Pulling on the two pieces of catgut draws the ureter well into the lumen of the bowel, and the two ends of catgut are now tied lightly, thus holding the ureter in the bowel. The opening in the bowel is now closed lightly about the ureter; care must be taken not to close it too tightly. One of the reasons for failure of this simple type of anastomosis is a cicatrix forming at the orifice, thus shutting off the ureter. In our series this simple method was used 27 times with two permanent fistulas, and four others were considered as unsuccessful. One reason for our failures was thought to be due to the ureter pulling out from the bowel. Shortly after we made a few such anastomoses, in a discussion of the situation with Dr. Brunschwig, he stated that he was using this method but used what he called a "patch" in addition, to relieve the tension at the site of the union and also to cover up the area of the anastomosis and make it more water tight. This simple procedure was next used by us, constituting our second method—the "dunking" method with a patch of peritoneum.

In this procedure the same technique as previously described is used but in addition a piece of peritoneum is left on the ureter when it is dissected out. This peritoneum or patch should be 3 to 4 cm. in length and 1 to 2 cm. in width. The possibility of using the "patch" in any type of anastomosis should be remembered when commencing the surgery as often, without thinking, the ureter will be dissected out of its bed without any peritoneum remaining attached to it. It is important to plan in advance so that the patch may be saved at the time of the ureteral dissection. The "dunking" anastomosis is done the same way as previously described, but the ureter is released about 1.5 cm. or more from the distal end of the patch so that after the ureter is well in the bowel the peritoneum can be sutured, raw surface down, onto the bowel distal to the opening in the bowel. Starting about 1 cm. beyond the opening in the bowel the patch is sutured with fine chromic catgut around the bowel stoma and back along either side of the opening for about 3 cm. The "patch" thus takes the tension off the "dunked" ureter and closes in and around the bowel orifice, assuring a tighter union. This dunking patch method has been used but five times and no measurement of success can be made as we have too few cases. In this group reanastomosis was necessary in one case.

The "dunking" method has not been considered as satisfactory and it was then determined to try the direct anastomosis method as suggested by both Nesbit and Cordonnier. This method we call the end to side, ureter to colon anastomosis and at the present time it is the one most preferred in the Vincent Memorial Hospital.

Inasmuch as we had seen the value of the "patch" technique in the "dunking" method we have continued, as far as possible, to use it in the direct anastomosis method (end to side, ureter to colon). The operation consists of preparing an uninjured piece of ureter with its peritoneal "patch." Again let us warn that saving the piece of peritoneum must be thought of early in the operation or it will not be available after the ureter has been freed. The piece of peritoneum should be of good size so that a real patch can be placed over the anastomosis. In this method a small opening is made in the bowel, as described, and the ureter prepared in the usual way. To make the small, normal ureter easier to join with the bowel, however, it is necessary to split the ureter by making an incision (fish-mouth) with a pair of scissors along the ureter, away from the side of its blood supply. This small fish-mouth incision opens the ureteral end so that there is more material to suture to the opening in the bowel. In most instances the anastomosis is made direct between the end of the ureter and the mucosa of the bowel but the inclusion of the serosa as well as the mucosa does no harm. Some surgeons choose to cut a small, round hole in the mucosa by trimming off some of the exuberant mucosa with a pair of scissors. The most important thing in all the various anastomoses is lack of tension, and this must be accomplished by choosing the correct site in the bowel so that the ureters are not on stretch and so that the bowel can sit easily on the posterior peritoneum and can be sutured to that peritoneum if so desired. Fine 00000 chromic atraumatic catgut is used as suture material and the proximal area of the incision in the ureter is sutured to the proximal piece of mucosa in the opening in the bowel. It is best to have the knots outside the lumen of the ureter, but this does not always seem to be easy to accomplish and we have found that an occasional inside knot does not matter. About seven interrupted sutures are made, and the union is completed. Before the final one or two sutures are placed it is important to note, by means of a probe, that the ureteral orifice is open. After the anastomosis is accomplished, if the opening in the serosa has seemed to be too large, it is closed with interrupted sutures of the same size catgut. Occasionally there will be too much of an opening in the bowel mucosa and it can be sutured together easily after the anastomosis has been completed.

The peritoneal patch which has been previously fashioned is now sutured, raw surface down, starting 1 cm. distal to the anastomosis, with interrupted catgut, beyond, lateral to, and proximal to the opening. This piece of peritoneum releases the tension on the ureter and makes the opening more water tight. The bowel can then be sutured to the posterior peritoneum, just on top of the ureteral exit from behind the peritoneum. If there is no peritoneal patch available it is often feasible to close in about the anastomosis with fat tabs or appendices epiploicae, so as to cover the area of the anastomosis. This operation, the direct anastomosis, can be done without the peritoneal patch but there can be no doubt that the patch is of great importance. Eighty-five of the 126 anastomoses in this series were accomplished by this method with 14 failures, and 8 necessitated further treatment of the urinary tract. In our hands the direct anastomosis with the "patch" is the best and most satisfactory type of anastomosis of the ureter and bowel.

Skin ureterostomies have been tried and found wanting. The care of such a urinary outlet has been found to be very difficult. We feel sure that this method does not solve the problem. Much better, if a ureterosigmoid anastomosis cannot be done, is the method of anastomosing the ureter into an isolated loop of ileum (Bricker) or into a cecal pouch (Gilchrist). Skin ureterostomies are now used only to save life.

Comment

The preoperative preparation of bowel is important in this type of surgery and we use Sulfathalidine, penicillin, and streptomycin in all cases. The bowel is not completely sterile, but in spite of spillage of fecal material occasionally at the time of operation no damage from infection has been observed.

The avoidance of tension is of great importance; without doubt the patch method relieves the tension at the site of the anastomosis. Suture of the sigmoid to the posterior peritoneum takes the tension off both bowel and ureter. The anastomosis heals well and the same percentage (10) of strictures were found in both the dunking and direct methods. This direct method allows for easier reflux of gas and bowel content up the ureter to the kidney, a source of continued bouts of pyelonephritis. (Parsons advocates doing a transverse colostomy above the anastomosis, thus necessitating two openings onto the abdomen, but with a clean and sterile sigmoid pouch for the ureterosigmoid anastomosis.) The spacing of the second ureteral anastomosis is occasionally difficult but with experience this problem is not too great. In most instances the anastomoses are placed about 1 to 1.5 inches apart and patches can be used over each. Occasionally it has been necessary to anastomose the ureter to the cecum and although considered as dangerous, as far as reabsorption of nitrogenous products is concerned, no deleterious effects have been noticed.

Ureters that are dilated and kidneys with poor function and noticeable hydronephrosis have been used in anastomoses and in most instances function satisfactorily. In four instances the kidney has been restored to full function and the hydronephrosis has diminished remarkably in size. Preservation of function is of great importance and should be sought for whenever possible.

In certain instances it was necessary to tie off a ureter. This is especially so when the kidney showed no function by intravenous pyelography before operation. Lately we have felt that even though no function is demonstrated the

TABLE I. URETEROINTESTINAL ANASTOMOSES IN PELVIC EXENTERATIONS: 68 CASES, 126 ANASTOMOSES

(One patient had bilateral double ureters, two had had ureteral transplantation prior to pelvic exenteration, eight ureters were ligated.)

METHOD	SUCCESSFUL	LEAKS	RE-OPERATION: NEPHROSTOMY AND TRANSVERSE COLOSTOMY	RE-OPERATION: REIMPLANTED	RE-OPERATION: TRANSVERSE COLOSTOMY	STRICTURE	RE-OPERATION: NEPHROSTOMY	RE-OPERATION: NEPHRECTOMY FOR STONES AND INFECTION	DIED EARLY	TOTAL NUMBER ANASTOMOSES	TOTAL NUMBER CASES*	RENAL DEATHS	PROGRESSIVE RENAL CHANGES (NO. OF CASES)	CLINICAL PYELITIS	IMPROVEMENT OVER PREOPERATIVE CONDITION
Dunking	16	2	1			4	2		5	27	15	1	1		
Dunking with patch	1	1		1		3				5	3		3		
Direct	65	5		2	3	9	3		6	85	45	3	9	5	4
Bricker	2								4	6	3				
Skin	3							1		3	2		1	1	
Total	87	8	1	3	3	16	5	1	15	126	68	4	14	6	4

*Some patients appear in column "Total No. of Cases" twice since different method of anastomosis was used on each side.

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kidney might come back, and such ureters are now transplanted into the bowel, with the hope that function will be restored.

In the course of following patients we have considered that long loop colostomies may be dangerous, especially in those patients who have been radiated. It is conceivable that a loop of sigmoid below the anastomosis that reaches into the pelvis and then has to rise up out of the pelvis to the colostomy opening may collect urine and, being heavy and full of urine, may break, rupture, and leak, creating a perineal fistula. The surgical relief of such a condition is difficult and not very satisfactory. It is important to have room to do the anastomosis easily but it must be assured that this heavy, urine-loaded loop does not form the bottom of the new pelvic floor. Danger from rupture is ever present.

Recurrent bouts of pyelonephritis are not uncommon in some of our patients with wet colostomies (6 cases). The formation of stones (5 cases) in the kidney and upper urinary tract is a real threat but on the whole the more we know about the surgical treatment fewer and fewer complications arise.

Certainly the attempts to save the patient with localized but extensive pelvic cancer have greatly stimulated the search for better and better methods of caring for the urinary tract.

Conclusions

1. A report is made of the methods of anastomosis of ureter to bowel used in the Vincent Memorial Hospital.

2. The use of a peritoneal patch is important to relieve tension.

3. Proper choice of the area of anastomosis to avoid tension is important.

4. The "dunking" method is good, but we have come to believe that the anastomoses after the methods of Nesbit and Cordonnier are more satisfactory.

5. Leakage, stricture, infection, and stone formation are the problems in ureter-large bowel anastomoses.

TABLE II. DUNKING AND DUNKING WITH PATCH METHODS. ANALYSIS OF CASES

Dunking Method, 15 Cases.—
- No. anastomoses—27 (One, direct and dunk method; two, ureters ligated on one side.)
  - Leaks—2 (One, unilateral leakage at autopsy and stricture on the other side. One, unilateral leakage at autopsy.)
    - Reoperation—1 (Nephrostomy. Transverse colostomy and second nephrostomy.)
  - Stricture—4 (One, bilateral stricture; one, stricture on one side and leak on other side.)
    - Reoperation—2 (One, bilateral nephrostomies.)
  - Successful—16 (Nine cases; one, direct anastomosis on one side.)
  - Died early—5 (Three cases.)
- Progressive renal changes—1 case
- Renal death—1 case
- Clinical pyelitis—0

Dunking With Patch Method, 5 Cases.—
- No. anastomoses—5 (One, skin ureterostomy on one side.)
  - Leaks—1 (One, unilateral leak.)
    - Reoperation 1 (Retransplanted successfully to cecum.)
  - Stricture—3 (One case, one side probably sealed off at autopsy; another case, bilateral stricture—cecum anastomosis worse than sigmoid.)
  - Successful—1 (One side only.)
- Progressive renal changes—3 cases (One clinically well.)
- Renal death—1 (May have been.)
- Clinical pyelitis—0

TABLE III. DIRECT ANASTOMOSIS, BRICKER, AND SKIN URETEROSTOMY METHODS. ANALYSIS OF CASES

Direct Anastomosis Method—45 Cases.—(One case had bilateral double ureters.)
No. anastomoses—85 (One, double ureters ligated on one side; one, dunk method on one side; four, one ureter ligated on one side.)
Leaks—5
Reoperation—5 (Two reimplanted successfully.)
(Transverse colostomy 2 cases, but one with bilateral leak
Stricture—9 (Six cases, three bilateral.)
Reoperation—3 (Bilateral nephrostomy—1 case; unilateral nephrostomy, 1 case.)
Successful—65 (Both sides in 28 cases, one side in 9 cases.)
Died early—6 (Three cases.)
Progressive renal changes—9 cases (Three on one side only, 2 with stones; 6 bilateral, two with stones.)
Renal death—3 cases (One other case might have been renal death.)
Clinical pyelitis—5 cases
Improvement over preoperative condition—4 cases

Bricker Method—3 Cases.—
No. anastomoses—6
Successful—2 (One case)
Died early—4 (Two cases)

Skin Ureterostomy—2 Cases.—(One case had dunk with patch method on one side.)
No. anastomoses—3
Successful—3 (Although one case had nephrectomy for stones and infection later.)
Progressive renal changes—1
Pyelitis—1

Already Transplanted Prior to Operation—2 Cases.—

Ureters Ligated—7 Cases.—(One had bilateral double ureters.)
(Two, dunking method on one side; 5, direct anastomosis method on one side.)

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INDICATIONS FOR AND RESULTS OF URETEROINTESTINAL ANASTOMOSIS IN GYNECOLOGY*

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DURING the years 1932 to 1953, inclusive, 64 patients were subjected to the procedure of ureterointestinal anastomosis on the Gynecological Service of the Johns Hopkins Hospital. The Coffey II[1, 2] technique with inlying ureteral catheters was used bilaterally with the 24 exceptions shown in Table I. For 10 of these, as can be seen from the table, the main reliance was on the principle of the Coffey II technique, but the procedure was modified to meet certain anatomical variations. Of the other 14 the anastomosis in 3 was in conjunction with complete pelvic exenteration, and in 5 of the others the operation was performed by a member of the visiting staff who prefers the Coffey I. Both of those done by the Jewett[3] technique were performed by Dr. Hugh J. Jewett.

TABLE I. TECHNIQUES USED OTHER THAN TYPICAL COFFEY II

A. Catheter Used in at Least One Ureter, 10 Cases.—	
Coffey II unilateral, no catheter other side	3
Coffey II bilateral, no catheter in third ureter	1
Coffey II unilateral, ligation opposite ureter	3
Coffey II unilateral, congenital absence of opposite kidney	2
Transvaginal implant with catheters	1
B. No Catheters Used, 14 Cases.—	
Coffey I, bilateral simultaneously	7
Coffey I, one at a time	2
Coffey I, unilateral with cutaneous ureterostomy opposite side	1
Hinman 7 suture	1
Jewett	2
Transvaginal without catheters	1

Indications

In thirteen of the patients the operation was performed for nonmalignant indications (Table II). In 51 patients the procedure was performed in conjunction with the treatment of malignant disease. The types of malignancy and purpose of the surgery may be seen in Table III. Anterior pelvic exenteration was performed 21 times, cystectomy or cystectomy and urethrectomy 10 times, and complete pelvic exenteration 3 times.

In Fig. 1 may be seen the distribution of the operations for the various indications by years of the period covered. It will be seen that most of the operations for nonmalignant indications occurred in the earlier years, while

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most of those for malignancy have been performed since 1947, reaching a peak in 1950, with a rather striking decline since, probably resulting from a loss of enthusiasm derived from observation of the poor results obtained.

TABLE II. NONMALIGNANT INDICATIONS FOR URETEROINTESTINAL ANASTOMOSES, 13 CASES

Urinary incontinence		9
Vesicovaginal fistula	6	
Urethral defects	2	
Exstrophy of bladder	1	
Cystitis		4
Encrusted	2	
Interstitial	1	
Chronic ulcerative	1	

TABLE III. TYPE OF CARCINOMA AND PURPOSE OF SURGERY IN 51 PATIENTS WITH MALIGNANT DISEASE

PURPOSE OF SURGERY	TYPES OF CARCINOMA		
	GENITAL* 24	BLADDER 21	URETHRA 6
Attempt to cure	18	15	2
For palliation only	4	6	2
To correct complications of previous treatment	2	0	2

*Cervix 22, Endometrium 1, Vagina 1.

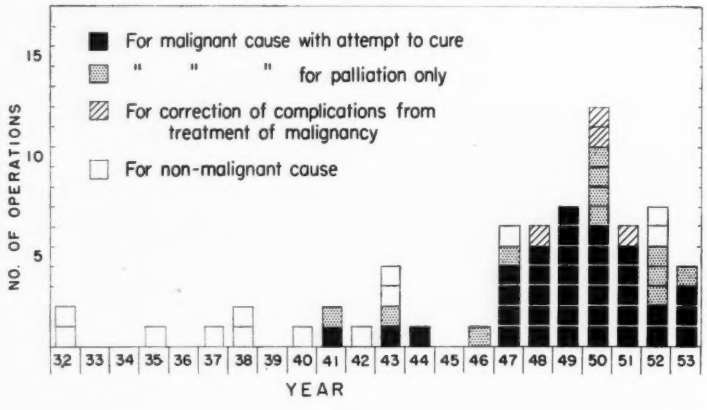

Fig. 1.

Results

The results of the procedures carried out may be seen in Fig. 2. They are not such as to create enthusiasm for this method of treatment. They are not greatly out of line, however, with results reported by others. Due to the variety of indications in our series it is not easy to find reports of comparable groups. If we eliminate two patients who died on the eighty-third day after operation, however, one from cerebral metastases and the other from thrombosis of the middle cerebral artery, and consider the 24 others who lived for less than three months as operative mortalities, we arrive at an over-all primary mortality of 37.5 per cent, with 15 per cent for the nonmalignant and 43 per cent for the malignant groups. This corresponds closely with the results tabulated in 1939 by Hinman[4] for 308 cases treated by the Coffey techniques. The over-all primary mortality in that group was only 29 per cent, but in 132 cases in which the indication was malignant disease, the primary mortality

was 47 per cent. Twenty-one of our patients were subjected to anterior pelvic exenteration, a procedure very similar to that termed by the urologists *radical cystectomy*. Of 46 patients treated by this method for carcinoma of the bladder Whitmore and Marshall[5] report death within the first year of 22, or 48 per cent. Dean,[6] reporting upon 99 consecutive patients subjected to cystectomy at the Memorial Hospital, states that 57 died in less than three years, and only 5 were living for more than three years.

Referring again to Fig. 2 we have considered the 39 patients who lived less than one year as complete failures, although some of those with advanced carcinoma who lived from six months to a year were certainly made more comfortable during their remaining months as a result of the procedure. The presence of 5 patients operated upon for nonmalignant indications in this group is the most disheartening feature of the series. For the 9 patients in this group and the 3 others who lived 12 to 14.5 months in whom the operation was performed merely to relieve intolerable symptoms without any further effort to cure the advanced malignancy, about all that was expected was accomplished.

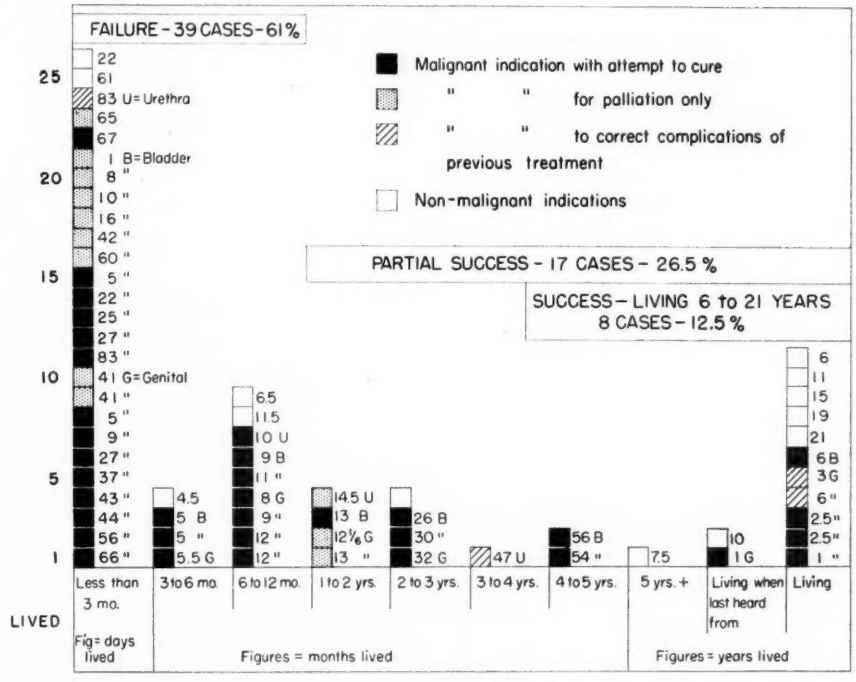

Fig. 2.

The one patient on whom the operation was performed for a nonmalignant cause and who lived a little more than two years had suffered for years from interstitial cystitis as well as pyelonephritis. There was bilateral calculus disease of the upper tracts, the calculi being removed at the same time as the ureteral transplants which were done at different times. Her half-hour phenolsulfonphthalein excretion was less than 5 per cent from each kidney, so that her outlook for prolonged life was poor, even had the operation not been performed. In the patients with advanced malignant disease who survived from one to five years we may consider that at least partial success was achieved. Those in whom the bladder was involved in the malignant process were certainly more comfortable than they otherwise would have been.

TABLE IV. CAUSES OF DEATH LISTED FOR 24 PATIENTS WHO DIED IN LESS THAN 3 MONTHS FOLLOWING OPERATION. TWO DIED AT HOME, THE CAUSE OF DEATH BEING QUESTIONABLE. AUTOPSIES WERE PERFORMED ON 14. MULTIPLE CAUSES OF DEATH WERE LISTED IN MOST CASES

LISTED CAUSES OF DEATH		AUTOPSY	NO AUTOPSY
Renal infection		13	0
Other infections		7	0
Abdominal and pelvic abscess	2		
Septicemia	2		
Peritonitis	2		
Meningitis	1		
Uremia		5	6
Venous thrombi and pulmonary embolism		4	1
Extensive metastases (cerebral 1)		1	3
Cardiovascular failure		4	2
Hemiplegia		1	1
Prolapse of bowel through vagina		1	1

TABLE V. CAUSES OF DEATH IN 24 PATIENTS WHO DIED 3 MONTHS TO 5 YEARS AFTER OPERATION. AUTOPSIES WERE PERFORMED IN 10 CASES

LISTED CAUSES OF DEATH	AUTOPSY	NO AUTOPSY
At home, cause unknown	0	2
Uremia or acidosis	4	2
Pyelonephritis or pyonephrosis	7	0
Extensive metastases	7	6
Cardiac failure	0	2
Cerebral accident	1	0
Meningoencephalitis	1	0
Acute pancreatitis	1	0
Inanition and malnutrition	0	1

TABLE VI. RESULTS OF PYELOGRAPHIC STUDIES

PYELOGRAMS	PREOPERATIVE	POSTOPERATIVE	
		EARLY	LATE
Normal	32	5	5
Unilateral dilatation	6	5	2
Bilateral dilatation	8	19	2
One side normal, other functionless (2 congenital absence)	9	0	0
One side dilated, other functionless	1	2	4
Reduced function one side, other normal	0	1	0
No visualization	1	1	0
Faint visualization one side, no visualization other side	0	1	0

Although our series adds 4 patients to those reported as having survived for more than ten years, the outlook for great longevity without severe renal damage is poor. In 144 patients operated upon for exstrophy of the bladder Harvard and Thompson[7] report a hospital mortality of 12.5 per cent, death from renal failure in 27 of 34 patients who died of known causes after leaving the hospital, and a history of pyelonephritis in 69.9 per cent of the survivors. Boyce and Vest,[8] in a review of the literature for the past sixty years, have found only 42 patients who had survived more than ten years. Half of these had lived more than twenty years but only seven more than twenty-five years. In all of those upon whom autopsies had been performed death was due to renal failure. Of the 21 patients still surviving, hydronephrosis was reported in 16, and in the other 5 definite information was lacking.

Autopsies were performed with available data in 24 of the patients in our series. The causes of death as obtained from autopsy reports and clinical

data are shown in Tables IV and V. In many instances, particularly for those in which the autopsy reports were available, several findings sufficient to cause death were listed. These tables, therefore, contain more listed causes than deaths. A comparison of Tables IV and V shows that in those patients who died early infection of various types and uremia were the most frequent causes of death, while in the patients who survived longer extensive metastatic carcinoma is listed as the most frequent cause, with infection second and uremia third.

Complications

Early postoperative complications militating against success were avulsion of anastomosis in 4 cases (3 bilateral), wound disruption in 3 (twice in one), intestinal obstruction in 2, and anuria necessitating pyelostomy in one patient subjected to a simultaneous bilateral Coffey I transplant.

Effect Upon the Kidneys and Renal Function

Evidence from the literature, some of which has already been cited, should leave little doubt that the procedure of ureterointestinal anastomosis cannot be undertaken without danger of renal damage from either obstruction or infection or both. In our series, of the 24 autopsies performed, there were only 2 in which no evidence of renal damage was reported. In Table VI may be seen the results of pyelographic studies. The finding of normal postoperative pyelograms in only 5 patients as compared with 32 in whom the preoperative studies were normal is further evidence that the operation cannot be performed without grave risk of some detriment to renal health. On the other hand, occasionally striking improvement in renal status is noted as a result of the procedure. The following case is a striking example.

A. B., aged 20 years, Negro, J. H. H. No. 273635, was first admitted in October, 1942, with complete encrustation of the bladder and a bladder capacity of only 15 c.c. Excretory pyelography at this time, Oct. 24, 1942, revealed normal upper urinary tracts (Fig. 3). Attempts at continuous irrigation of the bladder with Suby-Albright Solution G. through a two-way catheter were unsuccessful because of its small capacity. On Dec. 8, 1942, a suprapubic cystotomy was done in the hope that through-and-through irrigation could be accomplished. This procedure was also unsuccessful. On March 4, 1943, an attempted cystogram showed bilateral vesicoureteral reflux with marked bilateral hydroureteronephrosis (Fig. 4). This finding was confirmed by excretory urography on March 13, 1943 (Fig. 5). On March 19, a bilateral Coffey II transplant was performed by the senior author (H. S. E.), and the left tube and ovary were removed because of a small ovarian cyst. Early postoperative pyelograms, April 19, 1943, showed little change (Fig. 6), but the patient has remained well and excretory urography Sept. 12, 1949, and Oct. 12, 1951 (Fig. 7), showed very nearly normal upper urinary tracts. On Oct. 13, 1951, a total abdominal hysterectomy and right salpingo-oophorectomy were performed because of a right hydrosalpinx and right ovarian cyst. The patient was seen last on Jan. 14, 1954, is without complaints, works daily and apparently is in perfect health. Blood chemical analyses at this time were all within normal limits, but at times as shown have suggested mild hyperchloremic acidosis.

One cannot avoid intense disappointment when postoperative pyelograms show an excellent result from the ureterointestinal anastomosis but the rapid recurrence of carcinoma renders the situation hopeless (Figs. 8-13).

Considerable attention has been devoted in the recent literature to alterations in the blood chemistry resulting from the operation. The syndrome of hyperchloremic acidosis has been especially emphasized. This may be associated

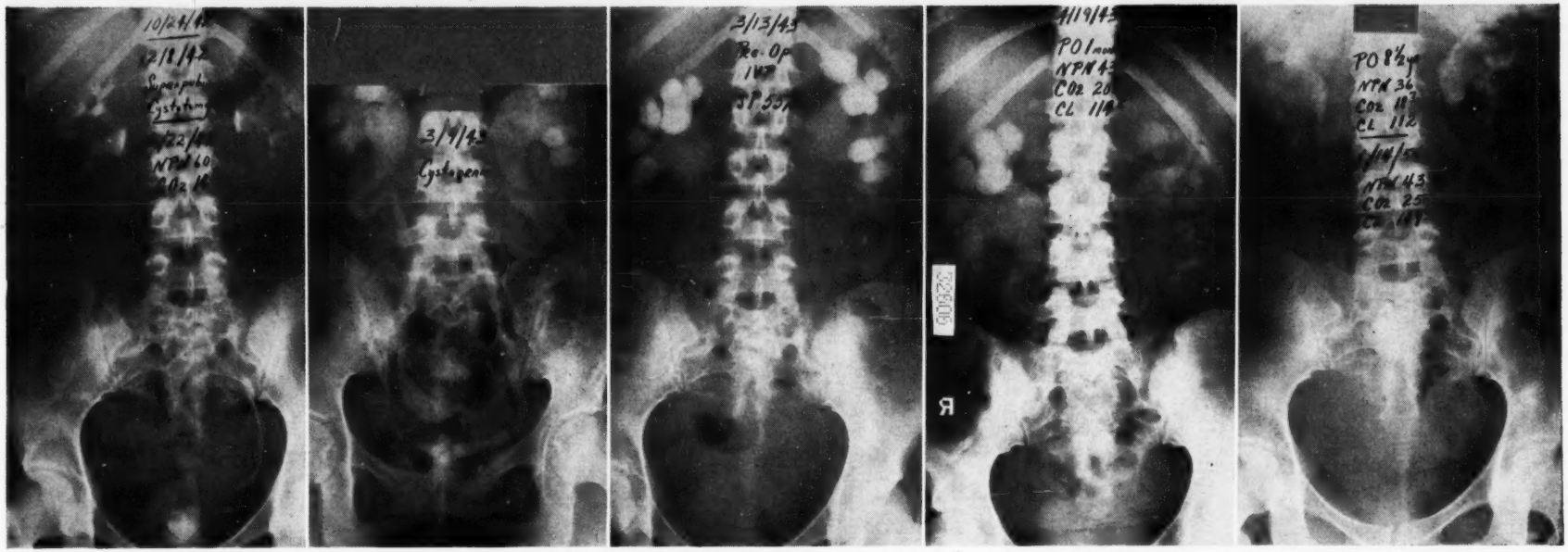

Fig. 3. Fig. 4. Fig. 5. Fig. 6. Fig. 7.

Fig. 3.—J.H.H. No. 273653, Negro, aged 20 years. Encrusted cystitis. Bladder capacity 15 c.c. Excretory pyelograms, Oct. 24, 1942.
Fig. 4.—Cystogram, March 4, 1943, on same patient as in Fig. 3. Suprapubic cystotomy had been done Dec. 8, 1942.
Fig. 5.—Excretory pyelograms on same patient as in Figs. 3 and 4, March 13, 1943, six days before ureterointestinal anastomosis.
Fig. 6.—Excretory pyelograms April 19, 1942, one month after operation in same patient as in Figs. 3, 4, and 5.
Fig. 7.—Same patient as in Figs. 3-6. Excretory pyelograms Oct. 12, 1951, eight and a half years after operation.

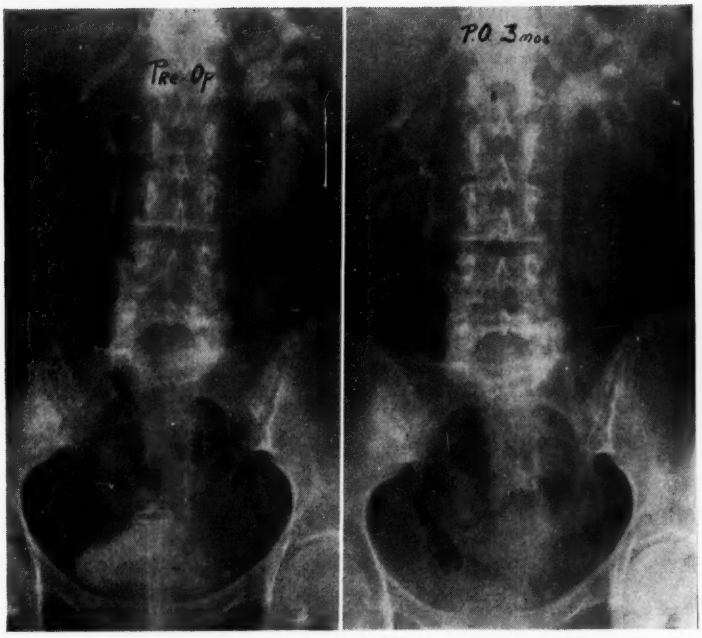

Fig. 8. Fig. 9.

Fig. 8.—J.H.H. No. 516801, white, aged 49 years. Infiltrating carcinoma of bladder. Preoperative pyelograms. Nonprotein nitrogen 25 mg. per cent, carbon dioxide combining power 25 meq. per liter, chlorides 105 meq. per liter. Coffey II, cystectomy, bilateral salpingo-oophorectomy and excision of cervix, Oct. 12, 1949 (Everett).

Fig. 9.—Same patient as in Fig. 8. Jan. 20, 1950, three months after operation. There was already evidence by palpation and biopsy of recurrent carcinoma in the rectovaginal septum.

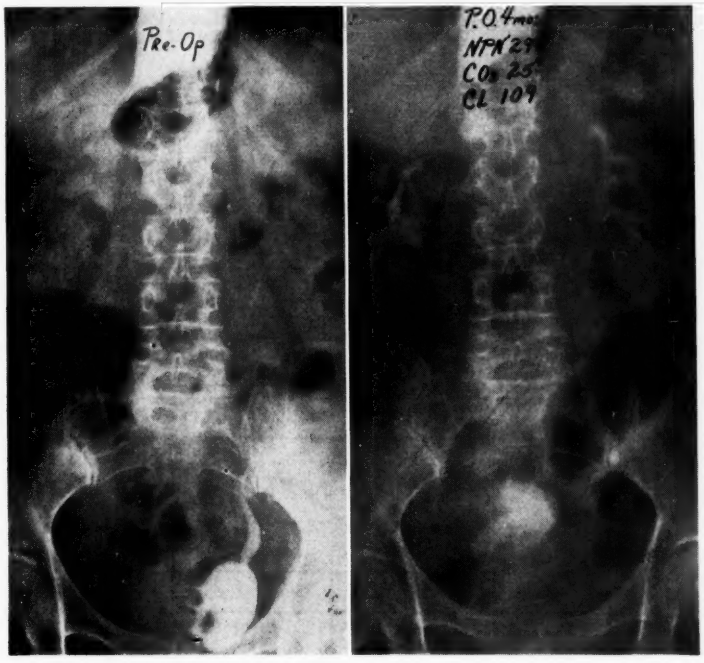

Fig. 10. Fig. 11.

Fig. 10.—J.H.H. No. 558125, white, aged 68 years. Infiltrating carcinoma of bladder. Preoperative excretory pyelograms, Dec. 6, 1950, showing obstruction and diminished function on right side. Coffey II, cystectomy, total hysterectomy and partial vaginectomy (O'Donnell) Dec. 12, 1950.

Fig. 11.—Same patient as in Fig. 10. Excretory pyelograms, April 13, 1951, four months after operation, essentially normal. Blood chemistry determinations were normal as shown. The patient died of recurrent carcinoma Aug. 16, 1951, eight months after operation.

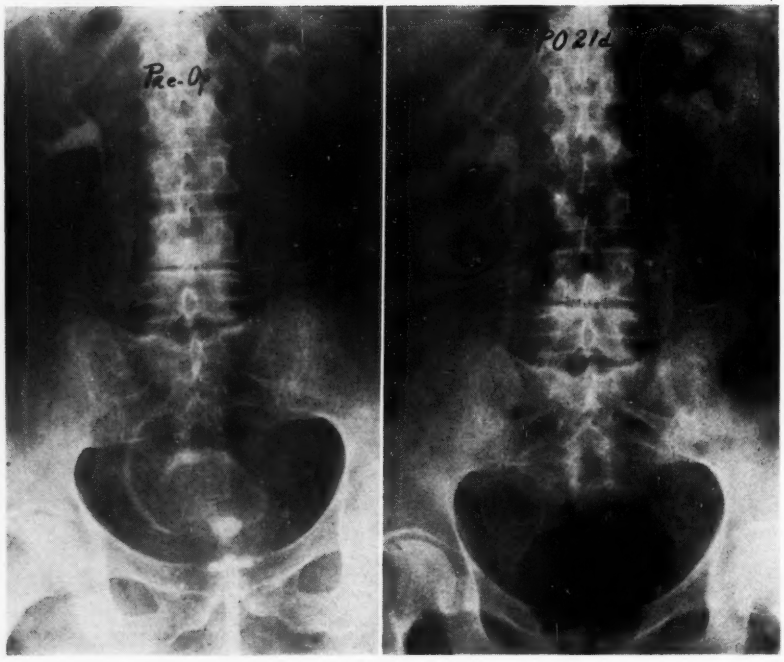

Fig. 12. Fig. 13.

Fig. 12.—J.H.H. No. 556744, white, aged 67 years. Carcinoma of bladder, infiltrating, papillary type. Excretory pyelograms Nov. 20, 1949, nine days preoperatively. Nov. 29, 1949, Coffey II, total cystectomy, total hysterectomy and bilateral salpingo-oophorectomy (E. H. Richardson, Jr.).

Fig. 13.—Same patient as in Fig. 12. Excretory pyelograms Dec. 20, 1949, three weeks after operation. This patient lived for 26 months and died of extensive carcinoma. This is one of the two patients in whom autopsy showed no evidence of renal damage.

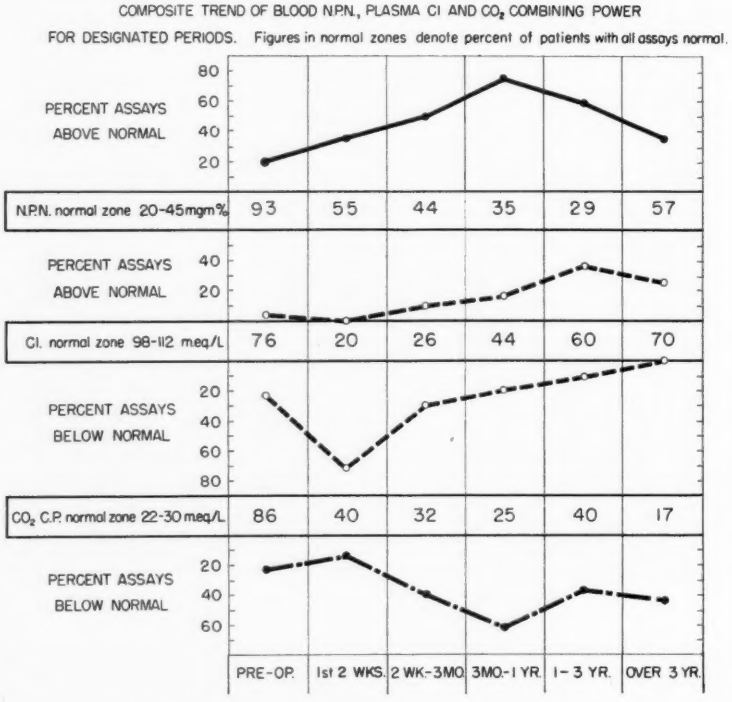

Fig. 14.

with an elevation of nonprotein nitrogen indicating severe renal damage, or it may be present with normal nonprotein nitrogen levels, in which case it has been considered to be the result of reabsorption of urinary chlorides from the bowel.

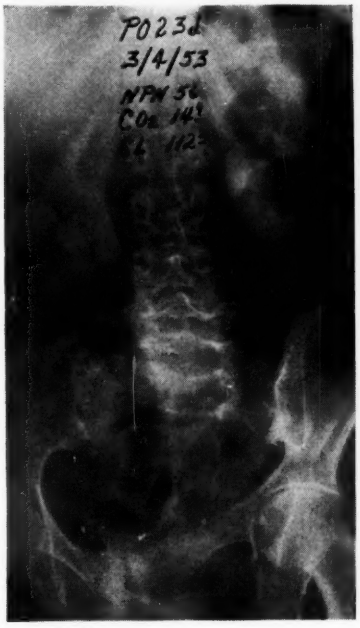

Fig. 15.

Fig. 15.—J.H.H. No. 628361, Negro, aged 80 years. Carcinoma of bladder. Coffey II done Feb. 2, 1953, for palliation only. Preoperative excretory pyelograms and blood chemical analyses were normal. Excretory pyelograms Feb. 24, 1953, twenty-three days after operation. The patient died March 14, 1953, forty days after operation.

Fig. 14 is an attempt to show the general composite trend of blood chemical analyses on those of our patients in whom such analyses have been done sufficiently frequently to be of value. The division of the earlier postoperative assays into two weeks, two weeks to three months, and three months to one year has been done for the following reasons: First, with the Coffey II technique the urine is shunted through the bowel by ureteral catheters for approximately the first two weeks. Second, one year represents the period in which 61 per cent of the patients died and three months that in which 41 per cent died. We believe that it is of importance that all blood chemical determinations have remained within normal limits in a significant proportion of the patients as long as they have been followed. The large proportion of low plasma chlorides in the earlier postoperative periods is probably accounted for by postoperative nausea and vomiting. The rise in chlorides and fall in carbon dioxide combining power signifying hyperchloremic acidosis definitely increases in the later determinations. This trend on the part of our patients is more in accord with the theory of Lapides[9] that hyperchloremic acidosis occurs only in association with damage to the renal tubular function resulting from pyelonephritis, than it is with that advanced by Ferris and Odel,[10] Odel, Ferris, and

Priestley,[11] and Mitchell and Valk,[12] that reabsorption of urinary chlorides through the intestinal mucosa is the more important factor. The excellent experimental work of Boyce,[13] however, leaves little doubt that reabsorption is an extremely important factor, and that the higher in the bowel the ureters are transplanted the greater the dangers from reabsorption.

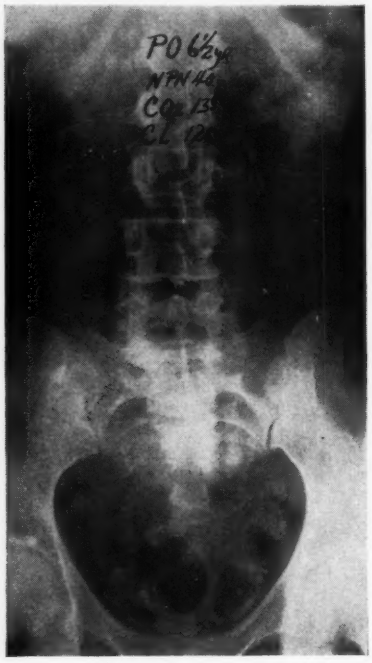

Fig. 16.

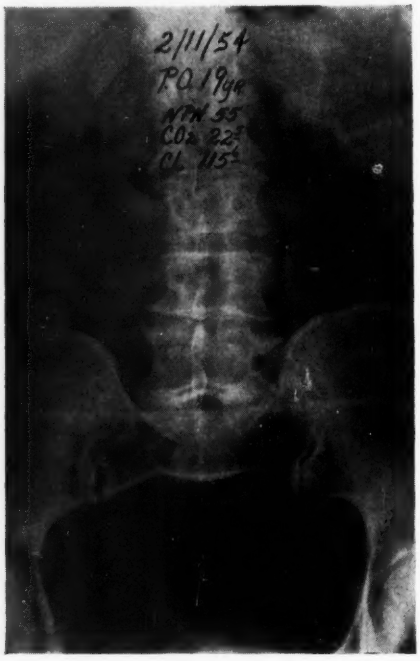

Fig. 17.

Fig. 16.—J.H.H. No. 330720, Negro, aged 46 years at time of operation. Diagnosis: total incontinence resulting from destruction of urethra by lymphopathea venereum. Coffey I, left, April 2, 1947, and right, Oct. 11, 1947, by Dr. R. W. Te Linde constituted the eleventh and twelfth operations attempting to relieve the incontinence. Excretory urography Feb. 4, 1954, shows no visualization of the right kidney and hydroureteronephrosis, left. Chemical analyses on the same date as shown indicate hyperchloremic acidosis, but the patient has no symptoms and is very happy with the result.

Fig. 17.—J.H.H. No. 107589, white, now aged 66 years. Excretory urography Feb. 11, 1954, eighteen years and eight months after transvaginal ureterorectal anastomoses for complete destruction of the vesicovaginal septum (Guy L. Hunner[14]). The right kidney failed to visualize two years after operation, the left still appears essentially normal. Except for occasional symptoms of mild pyelonephritis on the right side the patient has remained well. Chemistry determinations show hyperchloremia but no acidosis.

The fact that with the Coffey II technique the ureters are of necessity transplanted quite low into the rectosigmoid may account for the apparent delay in evidences of hyperchloremic acidosis. As a matter of fact, of 16 patients in whom sufficient blood chemical analyses were available to permit of reasonable conclusions, only 8, or 50 per cent, showed chemical changes consistent with this syndrome. Of the twelve chemical analyses consistent with hyperchloremic acidosis in these 8 patients, two were within three weeks after operation (Fig. 15), the others being from eight months to nineteen years (Figs. 16 and 17). In six of the 12 analyses the nonprotein nitrogen was also elevated, indicating renal damage.

Comment

The variety of indications for diversion of the urinary stream as illustrated by this report, together with the poor results as obtained by us and recorded in the literature, some of which has been cited, makes it evident that we are in great need of some safer procedure with which to accomplish this purpose. Cutaneous ureterostomy would accomplish nothing in most of the patients operated upon for nonmalignant indications, and in those suffering from malignancy merely adds social ostracism to their other misfortunes. We need therefore to continue our efforts to discover a safer and more satisfactory procedure for such urinary diversion. There has been no lack of such efforts in the past, but so far, with the available techniques, the advantages shown by one over others have usually been offset by other disadvantages. For example, tendency to stenosis at the ostium and within the bowel wall of ureters transplanted by the Coffey techniques is not so prone to occur with the direct mucosa to mucosa technique advocated by Cordonnier,[15] Nesbit,[16] and Hinman;[17, 18] but this technique is more likely to result in reflux of gas and fecal material from the bowel into the ureters and renal pelves (Weyrauch and Young[19]). Furthermore, the dangers of leakage and avulsion of this type of anastomosis are greater (Hinman[20]). The technique recently advocated by Leadbetter[21] appears to combine the advantages and eliminate the disadvantages of both the Coffey and the direct mucosa to mucosa methods. Indeed, in reporting the first 8 cases in which this method was used there was evidence of significant hydronephrosis in only one, and there had been no symptoms suggesting pyelonephritis. This report, however, was at the end of only one year. Jewett[3] in the early reports following the use of his technique showed excellent pyelographic results, but he now tells us that the later development of serious renal damage and the high incidence of hyperchloremic acidosis in those patients who have survived for long periods of time have been quite discouraging. We are anxious to hear what Dr. Schmitz has to report on the Gilchrist[22] technique. Reports in the literature are as yet too recent and too few to permit evaluation. Theoretically one would think that while it might reduce the incidence of renal infection, it would in no way reduce obstruction, and on the basis of the experiments of Boyce[13] might lead to more serious hyperchloremic acidosis than arises from anastomosis lower in the bowel.

Summary and Conclusions

The variety of indications for diversion of the urinary stream arising in gynecological practice and the poor results obtained with the present available methods make diligent search for improved methods imperative. When used in conjunction with the surgical treatment of advanced malignancy the present methods often make possible a more comfortable life for as long as the malignant process permits survival. For nonmalignant indications, however, the high primary mortality and late renal damage make the procedure by the presently available methods one to be undertaken only when all other measures of treatment have failed.

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THE "POUCH" BLADDER*

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THE extensive procedures employed in the present-day surgical attack on advanced carcinoma of the female genital tract pose a question of how to divert the urinary stream. Surgical procedures performed for carcinoma not involving the rectosigmoid, but in which the bladder must be removed, are best handled by implanting the ureters into the sigmoid. In our experience, when colostomy was also necessary, such colon implantation with the resultant wet colostomy proved annoying, and the already badly damaged urinary tract was subjected to further insult, which produced progressive destruction and final failure of the excretory system (Fig. 1).

Skin ureterostomy in our hands proved unsatisfactory due to constriction of the stoma, necessitating dilatation and frequent replacement of ureteral catheters. Such procedures were followed by fever due to ascending infection and furthered kidney damage and destruction. The apparatus necessary to collect the urine was annoying, and the patients were never satisfied (Fig. 2). Consequently the method has been abandoned.

We have since undertaken a study to evaluate other means of forming a reservoir for collecting the urine from the cut ureters and transferring it to the outside.

Many variations of the "pouch" bladder have been described.[1, 6, 7] In each instance the authors are impressed by either simplicity of construction, prevention of reabsorption of urine chlorides, absence of ascending infection, or patient acceptability. Although in our clinic we have confined our efforts to the wet colostomy, skin ureterostomy, or the ileocecal pouch, we are impressed with other techniques and believe they should be discussed at this time.

The ileocecal segment of Merricks and Gilchrist[7] has been employed by us in five instances. The earliest case will have survived three years on Sept. 28, 1954, and is progressing satisfactorily after numerous complications. The technique employed is that of the original authors and is as follows:

After the abdomen is opened through a right rectus incision, careful inspection of the entire abdominal contents is carried out. If the disease has not extended above the bifurcation of the iliac vessels, future exenteration is possible provided there is no fixation within the pelvis. It is our

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experience that the ideal situation for exenteration is in cases where bladder and/or rectum are invaded, but lateral spread of the disease has not as yet become attached to the pelvic fascias; where nodes are not palpated above the iliac bifurcation and there is no fixation of glands in the obturator canal. Hydroureter and hydronephrosis should be minimal, with function previously determined by the phenolsulfonphthalein test as adequate, which means a total excretory function equal to one functioning kidney.

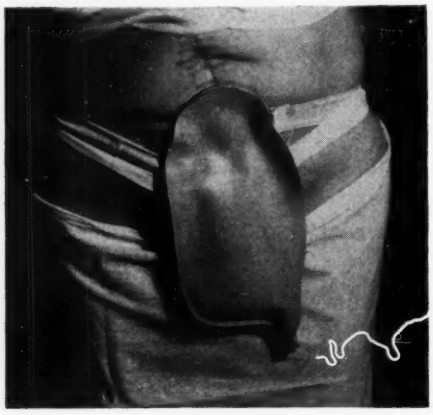

Fig. 1.—Wet colostomy.

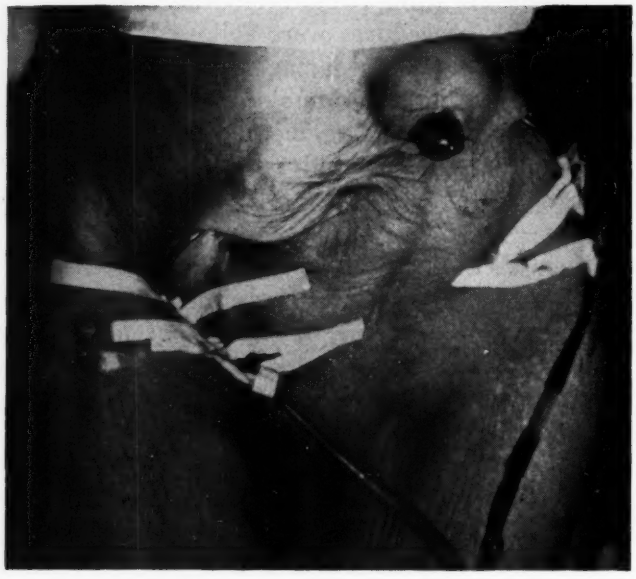

Fig. 2.—Skin ureterostomy.

If both kidneys are damaged beyond this degree the procedure carries a high risk and short-time survival of the patient, and is therefore not justifiable. At least seven to eight inches af ascending colon are utilized so as to obtain a capacity of 500 c.c. After closure of the distal and proximal ends of the divided colon, the ileum is amputated far enough from the ileocecal valve to ensure its reaching through the incision in the abdominal

wall (4 to 5 inches). This necessitates turning the ileocecal segment on its mesentery. An ileocolostomy is done to re-establish the continuity of the gastrointestinal tract. The last step is the implantation of the ureters into the pouch. This is performed by the Coffey technique of implantation.

Because of the complications encountered in Case 1, it is given in abstract:

CASE 1.—A 46-year-old gravida i, para i, was referred for treatment of recurrent carcinoma of the cervix. The history revealed that she had been essentially well all her life until December, 1948, when she developed a leukorrhea with associated low back pain. She consulted her local physician and was treated with chemical cautery of the cervix. Four months later, in April, 1949, the cervical lesion was biopsied and she was treated with intracervical radium in June, 1949, and again in November, 1949. Between the two radium

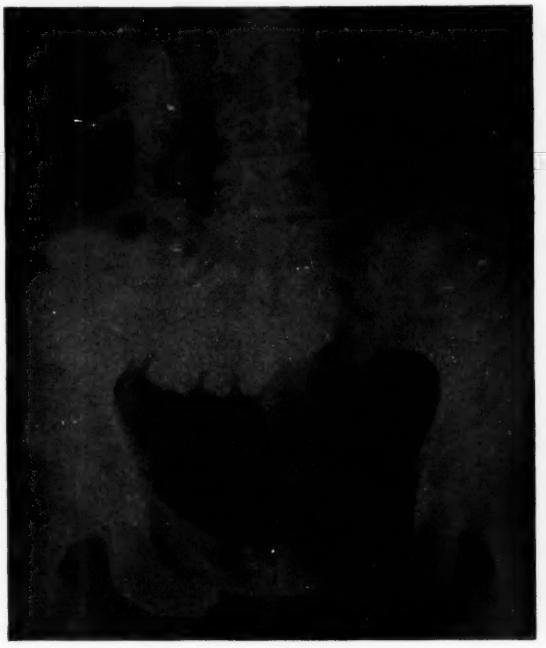

Fig. 3.—Gilchrist pouch. Right hydronephrosis.

applications she received a course of deep x-ray treatments to the pelvis. Because of lack of regression of the lesion, she was referred to our clinic for further therapy. She was admitted on Jan. 15, 1950. Her chief complaints at this time were anorexia, weight loss of 15 pounds, and urinary frequency and urgency. She also noted blood in the stools on frequent occasions. It was decided that the treatment of choice would be a radical hysterectomy and lymph node dissection. Cystoscopic and proctoscopic examinations were essentially negative for intrinsic disease. Bimanual examination revealed that the upper half of the vaginal canal was indurated and the right parametrial area was extensively involved with tumor tissue. On speculum examination, the cervix was found to be enlarged and necrotic with a deep crater lined with a greenish slough. On Jan. 21, 1950, a radical panhysterectomy and pelvic lymphadenectomy were performed. Pathological examination of the excised cervix revealed active carcinoma with evidence of previous irradiation. On the twelfth postoperative day fecal drainage from the vagina was noted. A diagnosis of rectovaginal fistula was made, and conservative therapy was instituted. The fistula remained open, however, and because of this a colostomy was performed on March 4, 1950. The colostomy

functioned well and she was discharged on March 19, 1950, fifteen days after the colostomy and twenty-seven days after the radical hysterectomy. Intravenous pyelogram on March 17, 1950, revealed the pelvis of the right kidney to be dilated as well as the upper part of the right ureter. The ureter also appeared kinked in the upper portion. Impression was early hydronephrosis with hydroureter on the right side.

On June 3, 1950, the patient was examined because she complained of involuntary passage of urine for the previous two weeks. Bimanual examination revealed a posterior opening into the bladder. She was observed for several months, but the vesicovaginal fistula failed to close and she was readmitted to the hospital on April 22, 1951. Biopsies taken from the edges of the rectovaginal and vesicovaginal fistulas revealed no cancer tissue. The patient was then taken to surgery and the upper portion of the vagina was closed over, which obliterated both fistulas. The patient was discharged from the hospital on the nineteenth postoperative day. She was voiding well, but there was still some urinary drainage from the vagina.

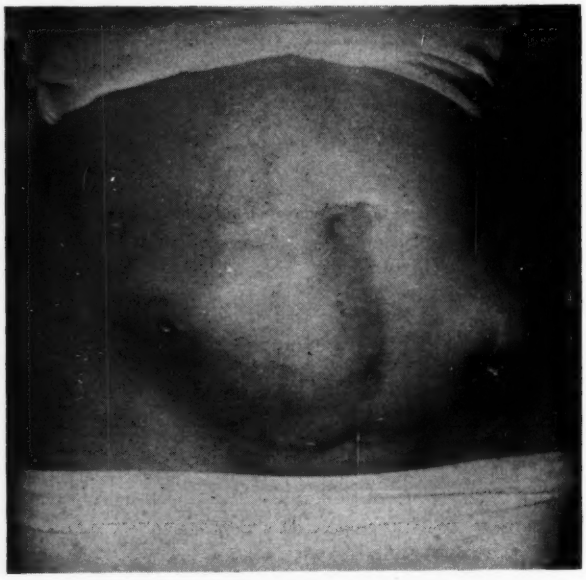

Fig. 4.—Stomas of Gilchrist pouch and colostomy.

The patient was readmitted to the hospital on Sept. 23, 1951, because of continued drainage of urine from the vagina since her discharge from the hospital in May, 1951. Intravenous pyelograms taken at this time revealed normal-appearing kidneys. On Sept. 28, 1951, a Gilchrist pouch operation was performed. On the third postoperative day the patient developed slight urinary drainage from the vagina. The Gilchrist pouch functioned well with the patient remaining continent up to four hours, but in spite of this she continued to have some urinary drainage from the vagina. It was the impression at this time, because of the difficulty of implanting the left ureter, that the left ureter had pulled away from the pouch and was draining into the peritoneal cavity, ultimately reaching the vagina. The patient was discharged on Oct. 14, 1951, the Gilchrist pouch functioning well, but the slight vaginal urinary drainage persisting.

The patient progressed fairly well until May, 1953, when she developed severe episodes of pain over the left flank. She was still having a slight amount of urinary drainage per vaginam. Intravenous pyelogram revealed a nonfunctioning left kidney. It was thought that the patient probably had enough left kidney function to drain a small amount of urine into the vagina which, with occasional blockage causing hydronephrosis and pyelitis, accounted for her present symptoms. On June 22, 1953, a left nephrectomy was performed. She had an uneventful postoperative course and was discharged from the hospital on July

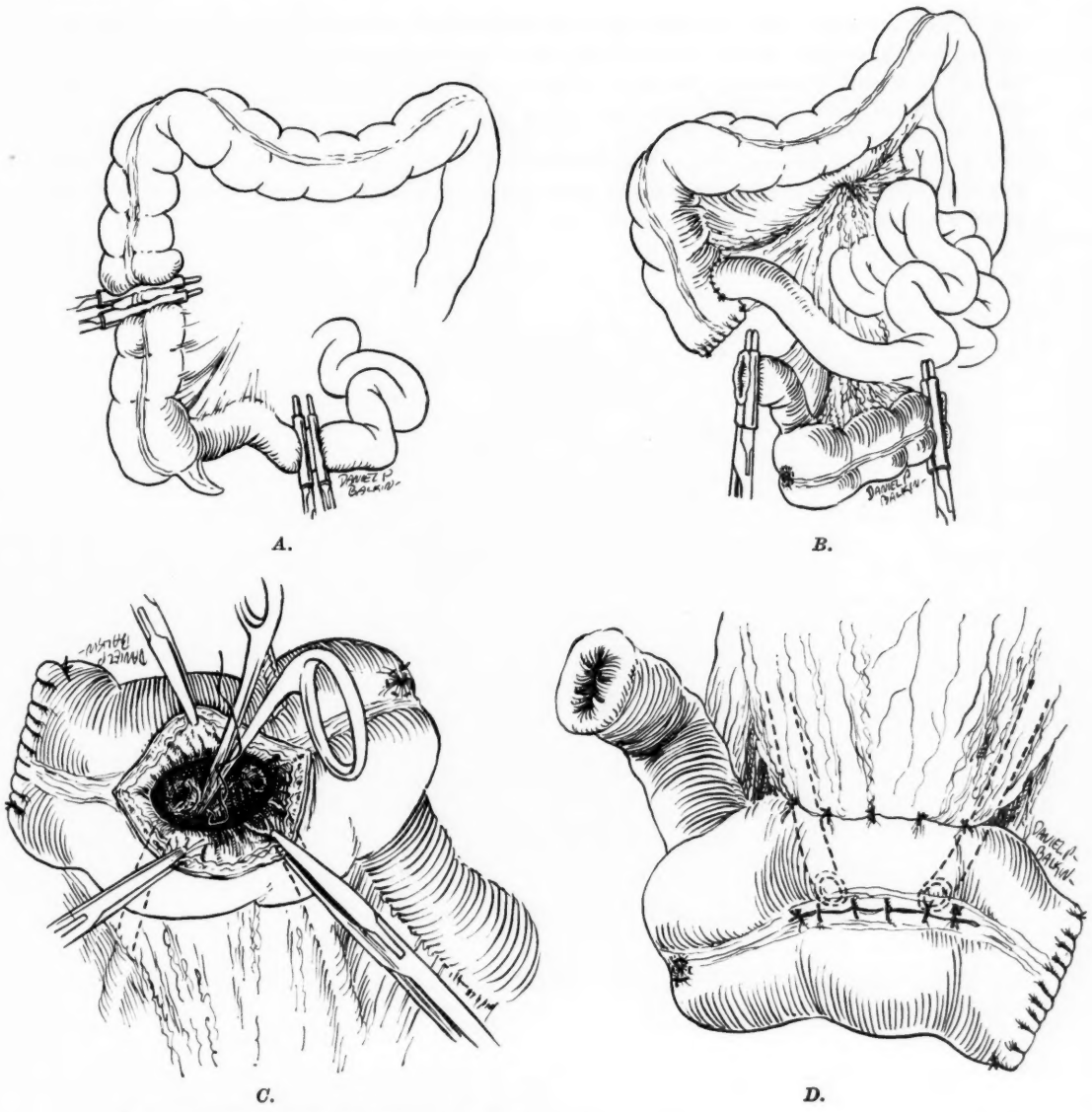

Fig. 5.—Development of ileocecal pouch.
A, Isolation of terminal ileum and cecum.
B, Rotation of closed and appendectomized pouch.
C, Implantation of ureter through posterior wall.
D, Closure and support of pouch.

1, 1953. Since that time she has had no further difficulty. She can manage her Gilchrist pouch quite well with perfect continence. There has been no further urinary drainage from the vagina. Her blood chemistry is normal and the pouch continues to function well. (Fig. 3). Fig. 4 demonstrates the stomas.

CASE 2.—This patient survived eight months without urinary tract complications, but died of progressive disease. Her pouch was continent.

CASE 3.—In preparation for later exenteration, the pouch was constructed as the first step. Because of oliguria and abdominal symptoms it was believed that the patient might be leaking urine intraperitoneally as in Case 1, and a secondary exploration was performed which she did not survive. There was no leakage and the patient might have survived if supportive measures had been continued instead of reoperation at this time.

CASE 4.—Numerous difficulties were encountered in constructing the pouch, especially in implanting the left ureter, the operating time being four hours. The patient succumbed several days postoperatively. Autopsy revealed adrenal and hepatic necrosis due to shock and prolonged hypoxia. The pouch was found to be functioning satisfactorily.

CASE 5.—The ileocecal segment was employed in this case because of a vesicovaginal fistula from active disease. The patient withstood the procedure well and is satisfied with her end result. Upper gland invasion found at the time of surgery precluded further attempts to perform pelvic exenteration.

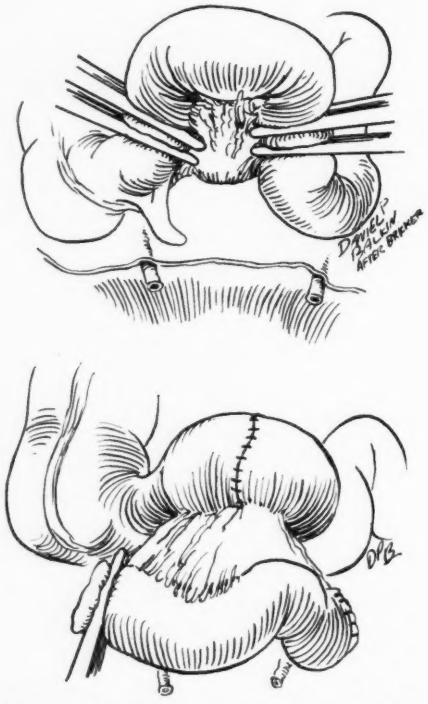

Fig. 6.—A six- to eight-inch length of terminal ileum is isolated approximately four to five inches from the ileocecal junction; an end-to-end anastomosis re-establishes gastrointestinal continuity; the proximal end of the isolated segment is closed. (After Bricker: S. Clin. North America 30: 1511, 1950.)

Our experience in these cases has demonstrated that constructing an ileocecal pouch is a formidable procedure which should be performed as a separate stage preliminary to pelvic exenteration. This permits greater ease of execution than when it is carried out as a secondary step at the time of exenteration. It is our opinion that the two procedures should not be performed at one time, for the combined operation is beyond the tolerance of these sick patients. Our technique of implanting the ureters has been altered in the last case to ensure greater security in the prevention of ureteral fistula and to adhere to the principles of Cordonnier[3] of approximating mucosa to mucosa, thus preventing: (1) postoperative leakage, (2) stenosis of the anastomosis, (3) urinary tract infection, or (4) obstruction of the ureter due to interference with normal peristalsis.

When the procedure was progressed to the stage of ureteral implantation, we now open the pouch with an incision in the mid-portion of the anterior wall (Fig. 5). Curved forceps are placed through the incision

against the posterior wall directly where the ureter lies. After the clamp is opened slightly an incision is made from the outer side and the forceps pushed through to grasp the cut end of the ureter and draw it into the pouch. Mucosa-to-mucosa suturing is now accomplished with greater ease and more careful approximation through the incision in the pouch. After both ureters are thus attached, the incision in the pouch is closed. The pouch is supported by attaching the cut edge of parietal retroperitoneum which has been cut across at the level of the promontory to expose the ureters.

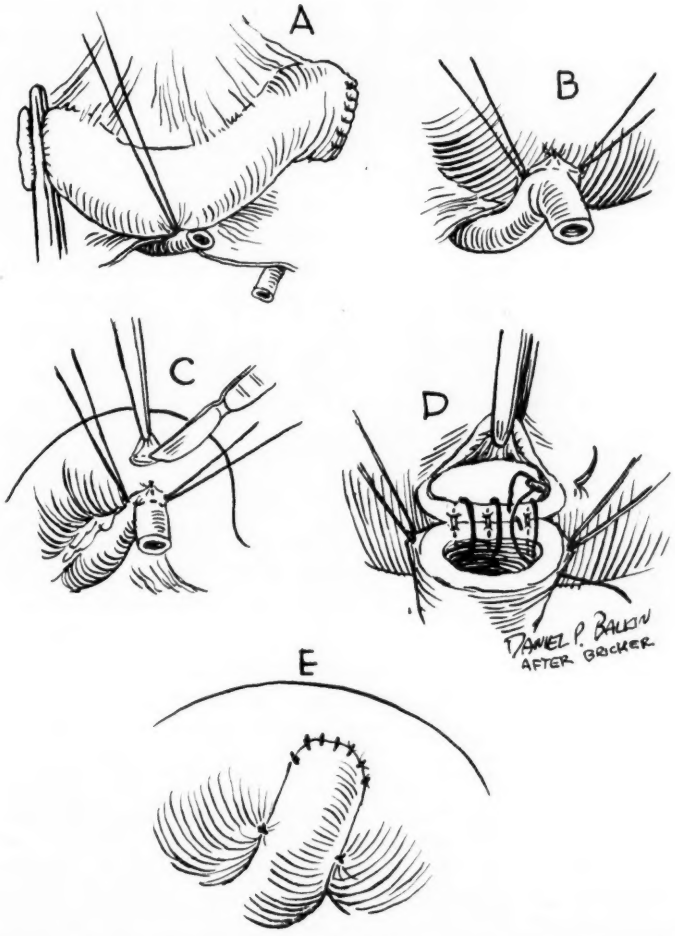

Fig. 7.—The ureters are anastomosed to the segment of ileum by an end-to-side, mucosa-to-mucosa approximation. (After Bricker: S. Clin. North America 30: 1511, 1950.)

All of our patients were continent and the patient who has survived two and one-half years has shown no absorption of urinary constituents.

Bricker,[1] not being able to make his patients with the ileocecal pouch truly continent, prefers to transport the urine from both kidneys to a single external stoma which is placed in a convenient location for adaptation of a Rutzen bag. He states, "An isolated segment of terminal ileum about six to eight inches serves this purpose perfectly, and in four recent cases the results are so gratifying that we consider the problem almost solved. Our

observations of the physiological effects of these isolated segments of ileum as to absorption of urinary constituents are negligible. Peristalsis in the segment favors rapid emptying and thus avoids stasis of urine."

Figs. 6, 7, and 8, taken from his article, illustrate the formation of the pouch constructed from the ileal segment.

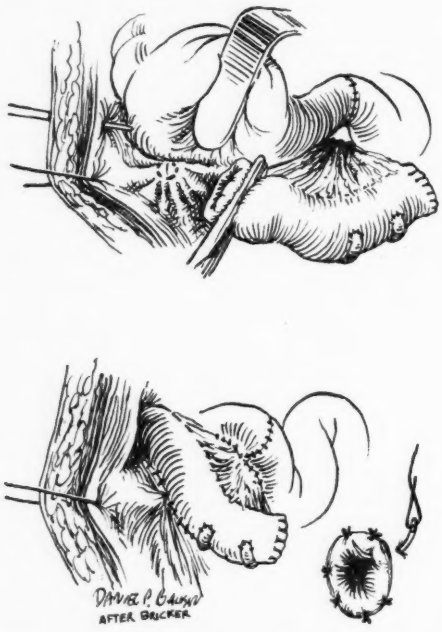

Fig. 8.—The open end of the ileal tube is passed through a stab wound in the abdominal wall, and its mucous membrane sutured to the skin with fine catgut sutures. The peritoneum of the right lumbar gutter is sutured to the segment of ileum and the space between the reanastomosed ileum and the mesentery to the isolated segment similarly closed. (After Bricker: S. Clin. North America 30: 1911, 1950.)

The Procedure.—A six- to eight-inch length of terminal ileum is isolated approximately four to five inches from the ileocecal junction; an end-to-end anastomosis re-establishes the gastrointestinal tract. The proximal end of the isolated segment is closed and the distal end is prepared for deliverance through the opening in the right side of the abdomen. The ureters are anastomosed. The right lumbar gutter is obliterated and the segment sutured to prevent herniation. The abdominal stoma is sutured to skin with fine catgut sutures. The operating time is forty-five minutes to one hour. There has been no instance of a breakdown of the anastomosis with the development of urinary fistula. Postoperative azotemia has not been a problem.

Other procedures[6-9] are but a slight departure from the methods described, but are too complicated to be acceptable for the badly damaged subject suffering with advanced carcinoma of the cervix and resultant urinary tract damage.

Comment

Surgical procedures aimed at giving relief to the woman suffering from far-advanced radioresistant carcinoma have been performed in our clinic in 85 instances. Our experience gained from this study has influenced us to change our indications for operability as well as the manner in which the urinary tract was handled.

At the outset of our study we attempted to subject all patients who did not have evidence of extrapelvic disease to the operation of pelvic exenteration as described by Brunschwig[2] in 1948. We soon discovered that edema of one extremity, indicating pelvic floor invasion, and obturator canal fixation or glandular extension above the common iliac nodes contraindicated the operation, for these patients were not relieved, or succumbed too soon after treatment to justify the effort.

In those patients in whom the bladder on palpation and after cystoscopic examination seemed free of invasion, we left the bladder intact; this, we found, posed many problems such as rapid appearance of active disease, or fistula due to radiation fibrosis and disturbed blood supply (Case 1); although in several instances where fistula occurred without disease we constructed a satisfactory pouch by closing the vaginal opening up to the urethra and then supplying the patient with a fashioned rubber stopper inserted into the urethra to control the flow of urine from the pouch. Three such patients have survived two, three, and four years, respectively. They are continent, satisfied, and have not had urinary complications to date. The high percentage of recurrence has caused us to remove the bladder more frequently. It is faulty thinking to believe that the bladder can be separated from a diseased cervix and invaded vaginal mucosa without leaving viable cells in the lymphatics or bladder muscularis. Although the bowel is not as closely allied to the vaginal walls we have been less conservative in the management of this structure.

Invasion or constriction of the ureter occurs relatively early in untreated or resistant carcinoma of the cervix. These patients therefore present a damaged excretory system and elevated nitrogen retention. Early in our studies we performed preliminary procedures such as skin ureterostomy to relieve the retention and restore the patient to normal excretion. Although on occasion a nonfunctioning kidney, so determined by intravenous pyelogram and phenolsulfonphthalein tests, will begin to secrete large amounts of fluid days after relief of the obstruction, this does not, however, indicate re-establishment of normal function, as such a kidney has lost its power of concentration and absorption. We have therefore discontinued such procedures as useless. If the patient is a poor operative risk on this basis, interference prolongs her suffering but adds nothing more.

We agree with Brunschwig,[2] Parsons,[8] Bricker,[1] and others that in those cases where the colon is intact, ureterosigmoidostomy is satisfactory, and we have one such patient now in her sixth year since removal of the bladder, radical hysterectomy, and pelvic node dissection.

The "pouch" bladder appears preferable to the wet colostomy, as in our study the damaged urinary tract withstood the added insult of wet colostomy poorly and four of our patients succumbed to ascending infection. Such patients are not always within reach of early antibiotic therapy, or succumb in spite of such treatment.

The ileocecal pouch as described by Merricks and Gilchrist[7] has proved satisfactory in our study as to continence, nonabsorption of urinary constituents, and ascending infection. It has been a formidable procedure in our

hands, with two operative deaths; experience and slight modification of the technique, however, should eliminate further operative fatalities. When undertaken as the preliminary step to exenteration, its execution is less difficult and permits careful evaluation of the patient as to suitability for further surgery.

The pouch of Bricker[1] seems to us less traumatic and time consuming, and we are now undertaking its evaluation. Our only objection has been the double Rutzen bag, one for the colostomy and the other for the urinary stoma. The fact that the stoma is on the right, away from the colostomy stoma, makes it preferable to the section of rectosigmoid as a pouch. Its close proximity to the ureters while still in their normal location is another asset. We believe, as does Cordonnier,[3] that the pouch should be brought to the ureters instead of bringing the ureters to the pouch.

Conclusions

1. Damage to the urinary tract occurs relatively early in patients suffering from carcinoma of the cervix.

2. As a result of such damage these patients are poor operative risks.

3. Diversion of the urinary tract into the sigmoid colon for those patients who present bladder invasion but an intact bowel is acceptable treatment.

4. Wet colostomy or skin ureterostomy was found objectionable in our series.

5. The "pouch" bladder of Merricks and Gilchrist has definite advantages, although it involves a formidable procedure requiring great care and meticulous execution.

6. The ileocecal pouch of Merricks and Gilchrist was constructed five times in this study with two operative deaths; all patients were continent.

7. The Bricker pouch seems less difficult to make and less traumatic. We are therefore undertaking its evaluation.

8. Other forms of constructing a urinary reservior seem too complicated to be practicable.

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THE UROLOGIC AND PHYSIOLOGIC ASPECTS OF URETERAL TRANSPLANTATION*

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WE IN urology believe that indications for diversion of the urine to the bowel include: (1) certain tumors of the urinary bladder; (2) exstrophy of the bladder; (3) certain cases of genitourinary tuberculosis; (4) irreparable injuries to the urethral sphincter; (5) irreparable vesicovaginal fistulas; (6) carcinoma of the uterus invading the urinary bladder; and (7) radiation necrosis of the urinary bladder.

I should like to discuss briefly *only* the first two indications: (1) tumors of the bladder and (2) exstrophy of the bladder.

Tumors of the Bladder

Since coming to the Brady Institute in 1946, I have followed quite closely the careful studies of bladder tumors made by my associate, Dr. Hugh Jewett. As you know, these studies have been concerned primarily with a comparison of survival rates in patients with bladder tumors subjected to various forms of surgical treatment *but* all graded in the same manner. Time does not permit a presentation of supporting statistics, but certain generalizations based on these data are in order: (1) The most important factor in the prognosis of any bladder tumor is the *depth of penetration* of the bladder wall determined by biopsy and bimanual examination under anesthesia. (2) Depth of penetration is of greater importance in prognosis than the histologic grade of the tumor. (3) Combining the histologic grade of the tumor with depth of penetration increases somewhat the accuracy of prognosis. (4) Any study which fails to consider depth of penetration is meaningless.

Based on depth of penetration, Dr. Jewett has divided all bladder tumors into four groups: (1) superficial, noninfiltrating tumors; (2) tumors which have invaded less than halfway through the bladder wall; (3) tumors which have gone more than halfway through the bladder wall but have not broken through into the perivesicular tissues; and (4) tumors which have extended beyond the bladder.

In the first group—superficial, noninfiltrating tumors—except when the tumors are innumerable as in benign papillomatosis, diversion of the urinary stream is never indicated, because any method which removes or destroys the tumor is curative. In benign papillomatosis, although cystectomy is curative, the high mortality associated with conventional forms of ureterointestinal anas-

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tomosis has caused many urologists to abandon cystectomy and to search for other means of destroying these multiple tumors. Thus, in England, Walton and Sinclair use radioactive sodium and bromine solutions contained within a balloon introduced through the urethra. Better results have been obtained with Br^{82}. It is reasonable to assume, however, that as methods of urinary diversion are perfected many of us will again resort to cystectomy.

It has been our experience at the Brady in dealing with the second group of tumors, those which have invaded less than halfway through the bladder wall, that segmental resection is as effective a method of treatment as total cystectomy. Of course, the location of the tumor will determine if segmental resection is possible. In doing a segmental resection we do not hesitate to reimplant either or both ureters, but if the tumor lies close to the bladder neck, especially in women, segmental resection may well lead to urinary incontinence. Consequently, in these cases it is not done.

In the third group of tumors, those which have extended deep in the bladder wall but not through, again segmental resection, when possible, has been as effective as total cystectomy.

In the last group of tumors, especially if positive nodes are found on abdominal exploration, even exenteration fails to cure. Dr. Victor Marshall tells me that he has given up the operation of exenteration if on abdominal exploration gross involvement of the lymphatics is observed.

In concluding this phase of the subject, I cannot help but add that, in spite of Dr. Jewett's work, which shows that in most instances segmental resection is as effective as total cystectomy, there are still many cases which would be best handled by cystectomy provided methods of urinary diversion are perfected. Certainly there is considerable evidence for the existence of a carcinogen contained within the urine which will continue to act on any remaining bladder epithelium. Multiple tumors, whether benign or malignant, continue to constitute a real problem.

Exstrophy of the Bladder

This continues to be a problem of great magnitude, and, as you know, surgical treatment has consisted of either an attempt at plastic repair or, more commonly, excision of the exstrophic bladder, ureterointestinal anastomosis, and repair of the epispadias.

The number of cases of successful reconstruction of the bladder are few. On several occasions Dr. Hugh Young nearly succeeded. The last patient on whom he reported in 1942, in whom success seemed assured on discharge from the hospital, later returned with a small vesicoabdominal fistula and some retention. The last report in this case was furnished by her physician in June, 1951. The essential part follows: "She goes to school daily, but has to be catheterized night and morning. She does not have any leakage but is unable to empty her bladder voluntarily."

In 1952, Drs. Sweetser, Chisholm, and Thompson reported one case: "The child can void well from the normal urethral meatus on the glans with a good

stream, though there is a little leakage under stress only from a pin-point fistula at the base of the penis. Panendoscopy showed a good bladder of about 50 c.c. capacity with a satisfactorily closed outlet."

I have had no success in closing these bladders but, then, attempts have been few. During the last year I have been encouraged to try again because of one near success and one complete success in two patients with complete epispadias with incontinence subjected to plastic revision of the vesicle neck. Both had been operated on before without benefit. Admittedly, urinary control is just one of several problems in the surgical correction of exstrophy, but it is a major one.

As stated earlier, most cases of exstrophy have been treated by excision of the bladder, repair of the epispadias, and ureterointestinal anastomosis. The largest reported series of cases so treated from one institution is that of Drs. Harvard and Thompson of the Mayo Clinic in 1951. Of 198 patients with exstrophy of the bladder seen between 1912 and 1946, 144 were treated by ureterointestinal anastomosis. In 133 of these the Coffey-Mayo technique was used. Ninety-eight patients were traced who had been operated upon at least five years before. Survival rates were 86.7 per cent at 5 years; 74.1 per cent at 10 years; 52.1 per cent at 20 years; and 50 per cent at 30 years. Postoperative mortality was 10.5 per cent. Pertinent to this discussion, well over 60 per cent of postoperative deaths were of renal origin, and renal failure was the cause of 65 per cent of the deaths that occurred after patients left the hospital. A little over two-thirds of 69 patients who survived operation and were living on Jan. 1, 1947, gave evidence of having pyelonephritis. These authors predicted that the advent of newer antibiotic and chemotherapeutic agents would do much to reduce disability but would not solve the whole problem. Their predictions were right for in almost an identical series—also from the Mayo Clinic—79 per cent developed hyperchloremia and 80 per cent developed acidosis. That this is not an unusual complication is evidenced by many reports. For example, this year Dr. Brunschwig reports acid-base and electrolyte imbalance in the majority of cases operated upon by him, and Drs. Garrett and Mertz found hyperchloremia of some degree at some time in all their patients and reduction of alkali reserve in over 75 per cent.

Physiologic and Biochemical Aspects of Ureterointestinal Anastomosis

Let us leave the subject of exstrophy, and, in conclusion, consider briefly the physiologic and biochemical aspects of ureterointestinal anastomosis. Both are of extreme importance, and it is safe to say that a study of both has contributed greatly to the development of newer and safer techniques and to rational medical management once ureterointestinal anastomosis of most any type has been done. In so saying, I do not mean to minimize the splendid anatomic studies which have contributed so much toward obviating obstruction and leakage at the site of the anastomosis.

The complications of ureterointestinal anastomosis include not only the hazards of a major abdominal operation, but certain sequelae peculiar to the

anastomosis of the urinary to the intestinal tract. Excluding certain anatomical considerations these problems are: (1) electrolyte imbalance and (2) renal insufficiency. Both often co-exist.

Electrolyte Imbalance.—The exact mechanism of production of hyperchloremic acidosis, so commonly a sequel to conventional forms of ureterointestinal anastomosis, is unknown. One school, supported by Odel, Valk, Bohne, and others, believes that the mechanism relates only to intestinal absorption and not to renal function. Another, supported by Lapides, Doroshow, and others, presents evidence to show that the primary cause is renal insufficiency. Still another believes that both absorption from the bowel and renal insufficiency are responsible.

Time does not permit presentation of data to support these several views, but from these various studies certain important generalizations can be made: (1) All human beings reabsorb chloride, sodium, and ammonia from the bowel. (2) Absorption of such substances is greater in the upper large bowel and small intestine than in the lower large bowel. (3) The larger the bowel reservoir, the greater is the reabsorption. (4) The longer the urine is retained in the bowel, the greater is the reabsorption. (5) Severe renal insufficiency alone may predispose to the production of acidosis or may aggravate acidosis once it develops. (6) Renal tubular acidosis may co-exist in a patient with a ureterointestinal anastomosis.

Renal Insufficiency.—Earlier in the hour data were presented in support of the contention that some degree of renal insufficiency is present in the vast majority of cases of conventional ureterosigmoidostomy. In this regard Lapides states that he has never seen a normal kidney at autopsy following this procedure. Whereas obstruction at the site of anastomosis is often at fault, it is my opinion that more commonly infection is responsible, such infection resulting from fecal contamination.

How can we utilize these principles?

Dr. Meigs has already described the evolution of ureteral transplantation and Dr. Schmitz the "pouch" bladder. I trust what I have to say in conclusion will not be overly repetitious.

Conclusions

First, diversion of the fecal stream seems to offer the most effective way of overcoming infection.

Second, obstruction at the site of anastomosis must be eliminated by the actual transplantation technique. This can be accomplished by the direct method and probably by others.

Third, the bowel reservoir receiving urine should not be too large.

Fourth, the bowel reservoir should either empty continuously or be emptied frequently.

Can these principles be incorporated into one operation? They can and have been. Thus, Kinman, Sauer, Houston, and Melick advocate proximal colostomy and implantation of the ureters into an excluded rectosigmoid pouch.

In their experience this type of procedure has worked well. One possible disadvantage, in addition to colostomy, is that the rectosigmoid reservoir is not continuously emptied and hyperchloremic acidosis has occurred.

Wells, Bricker, Cordonnier, and others advocate transplantation of the ureters into an isolated ileal segment. By using the ileal segment merely as a conduit and not as a reservoir for urine, a short piece of ileum can be used which furnishes a small absorbing surface and minimizes electrolyte absorption. Recently, Eiseman and Bricker, reviewing their results with this procedure, report no cases of hyperchloremic acidosis.

Last, Dr. Mark Ravitch and your speaker have been impressed with the fine result obtained following transplantation of the ureters into an isolated sigmoid loop the exterior of which was covered with skin.

The child in this case, when first seen with exstrophy of the bladder, a repair of which had been attempted, also had incontinence of liquid feces as a result of attempted repair of an imperforate anus. His renal function is now excellent, his electrolytes have always remained normal, and he has required no medicines in the form of antibiotics or chemotherapeutic agents for infection or bicarbonate and low-salt diet for hyperchloremic acidosis.

Discussion of Forum: The Ureter

DR. TE LINDE.—Before we start to pick the brains of these Quiz Kids, I would like to make a few remarks. I had the privilege of seeing these papers before they were read here and I have tried to note those things in which the four speakers are in agreement and then some of the points of disagreement.

First of all, they all agree that transplantation of the ureters into the bowel or taking care of the urinary tract by any other than the normal method is a formidable procedure. There is a high mortality and the results are not perfect. I think they all agree—at least the gynecologists do—that the success of exenteration depends upon the fate of the urinary tract as well as freedom from recurrence of malignancy. Also cutaneous ureterostomy is quite unsatisfactory in the eyes of these four men.

Dr. Meigs has presented a concentrated experience since 1948. He includes 68 cases, all associated with exenteration for pelvic carcinoma. He has concerned himself mostly with techniques, and concludes that direct mucosa-to-mucosa anastomosis is the superior method, using a bit of peritoneum as a patch. Of 126 anastomoses done on 68 patients, the anastomosis seems to function properly in 102, but we must remember in evaluating this report that not a great length of time has elapsed. He has concluded, however, that with improved techniques their results have improved.

Dr. Everett's experience is about the same over a longer period of time; he presented 64 cases from 1932 to 1953, and it is interesting to note the indications for which these operations were done in his clinic. At first a great many were done for serious but benign disease. After this, there was some enthusiasm for exenteration which reached its peak in 1950. Since that time there has been a gradual decline in enthusiasm. I think the greatest value of Dr. Everett's report is the long-term follow-up. It is noteworthy that just half of his cases—32 out of 64—had normal pyelograms preoperatively but only 5 out of 64 had normal pyelograms postoperatively. He does report, however, that 4 patients have survived ten years.

Dr. Schmitz reports on the ileocecal pouch in 5 cases with complete exenteration. Of these, there were two deaths, one from progressive carcinomatosis; one of his patients is progressing well as far as the urinary condition is concerned but she has carcinoma, and one of his patients is well and comfortable three years later but she had a stormy time of it.

Dr. Scott gives the urologist's point of view and he made three points: The first is that the pathologic physiology is a very important aspect of this subject. Second, the decision which the urologists have made in connection with carcinoma of the bladder may have a bearing on our future decisions in malignancy of the pelvis. They conclude after long experience with complete cystectomy that if the carcinoma does not penetrate through the bladder, the patient does just as well with segmental resection as with more extensive surgery. They further conclude that, when carcinoma extends beyond the bladder, exenteration is hopeless, which is a different point of view from that which some gynecologists hold for other pelvic malignancy. Finally, he reported one successful case in which ureteral transplantation was done in an isolated segment of the sigmoid.

The discussion is now open.

DR. HOWARD TAYLOR, JR.—Is there a statistical difference in the end results of these techniques?

DR. MEIGS.—The percentage of "dunking" failures was the same as the direct anastomosis failures. I think we have more leakage in the dunking operation than with the other.

DR. TAYLOR.—If there is no evidence that any technique is better than the others, is not the quickest method the best?

DR. MEIGS.—I think we do better with our direct anastomosis than with the dunking technique.

DR. TAYLOR.—Suppose we do this with exenteration. Under those circumstances is it not true that the best method is of secondary importance to the method that is quickest?

DR. SCOTT.—Yes, but in exstrophy the better the type of anastomosis and the more thought given to it, the longer the individual will live.

DR. MEIGS.—The fact that we do many more by direct anastomosis than by the old dunking method in itself means that we feel that we are getting better results, although I cannot prove that. It is difficult to prove it statistically, but I think we all feel the same. It is not because it is more difficult; it is not difficult really, it is quite simple.

DR. LAWRENCE WHARTON.—If the results were broken down so that you could tell whether a certain number, for example, had fistulas and others were operated upon for hopeless carcinoma, the opinion might be different in regard to this operation and the results might be different. In benign conditions, your cure rate has been much higher than in the malignancy group. I feel that in presenting a subject like this, if you could give figures in cases of benign conditions separated from malignant conditions, the results would be different.

DR. EVERETT.—I have done that but I consider that my group of nonmalignant indications is too small to be of value; there were only 13. I might add that four patients who had malignant disease apparently were cured of their malignancy by operation, but if we consider just the 13 nonmalignant cases, there were 5 deaths and that is a high percentage.

DR. WHARTON.—I get the feeling that the operation should almost never be done, and I must state that in my practice that is not true. Two weeks ago I saw a woman who had just come back from a hunting trip who had had a hopeless fistula from radium theraupy. I could not close the fistula but nine years ago I had implanted both the ureters, using the method of Lanman. Her pyelogram is normal.

DR. MEIGS.—This is a modification of the Coffey I operation.

DR. WHARTON.—I can show you slides of that technique; it is the simplest one I have used and it gives good results. There is nothing new in this at all. It is a Coffey

technique and is a very simple operation. You can do both sides in an hour. The sigmoid is exposed and the ureter is dissected up. I put a catheter in, after lifting the ureter up and freeing it, to divert the stream during the operation. Then an incision is made in the sigmoid opposite the ureter where the sigmoid can be brought back to the ureteral bed. Then the dissection in the sigmoid is carried down to the lining of the intestinal wall; you may get into the lumen but that does not make much difference. The idea is to get to the submucosa through the peritoneum. The ureter is laid in this trough and is buried by interrupted sutures. A hole is made in the intestinal wall and silk sutures are placed through the end of the ureter and brought out through the wall of the intestine. Those sutures are tied and the peritoneum is closed over the ureter. I have had no serious difficulties with that method. My inexperience led me to do a pyelotomy in one patient who had not put out any urine for three days. If I had waited twelve hours, I would have found plenty of urine coming through. One woman had obstruction of the intestine at that point and we found a small extravasation of fluid, but that was all. Those are the only complications I have had. Two women died. One week before death one woman had a normal pyelogram and she died of inanition for some other reason. I do not say that this method is perfect, but I have seen too many people greatly relieved in cases of hopeless fistulas by a simple procedure like this to say it is too dangerous to do.

DR. SCOTT.—I think the figures of Dr. Thompson from the Mayo Clinic show 50 per cent of the patients with exstrophy living after some thirty years. On the other hand, I recall that recently Dr. Marshall said he is doing less and less of ureterosigmoidostomy and more cutaneous ureterostomies in association with the operation of exenteration. And I remember two years ago in this same room Dr. Colston said he had done his last ureterosigmoidostomy for exstrophy because of poor results. Two years ago in Boston, Dr. Colby reviewed his results in benign papillomatosis; the five-year survivals were 20 per cent after cystectomy and the deaths were renal deaths. I think we have to face this, in spite of the occasional good result, and we have to attempt to analyze the situation. The procedure which Dr. Wells and Dr. Bricker have devised makes sense. How well it will stand up in time no one knows.

DR. TE LINDE.—Have you had a primary mortality with your procedure, Dr. Wharton?

DR. WHARTON.—No. The earliest death was 11 months afterward and she was a person in her sixties. She had a complete absence of the sphincter. Kelly had done an operation upon her when she was six years old. She was completely incontinent. I do not think one should do operations of this sort in people so old except in certain circumstances, and I thought this was one. She lived 11 months and died of inanition. Her intravenous pyelogram was normal one week before she died. She did not die of renal insufficiency. I think the operation is one which cannot be done or should not be done except in conditions which are insufferable. I think the people in whom I have done this for complete incontinence would rather be dead than continue the way they were, and we have succeeded in making them well and comfortable. In 1941, I operated upon a woman who had had thirteen operations for fistula, and she is still living and normal. One year after operation she wrote me a letter, wondering why in the world this last operation had not been done instead of the thirteen previous ones.

DR. THOMAS C. PEIGHTAL.—What are the end results of this pouch operation? Have they gone long enough to know anything about that?

DR. SCHMITZ.—I think we sometimes lose sight of the fact that in patients afflicted with carcinoma, we are starting out with a damaged urinary tract. Carcinoma extends laterally and involves the ureter early. We have hydroureter and hydronephrosis and improper function to begin with, and the question is how to select the patient whose urinary tract will stand the trauma of implantation. Very often where you have poor function on one side and you do a ureterostomy or implantation, urinary flow begins but that kidney has

lost its function of concentration and the patient is putting out water. That is entirely different than when we deal with a benign disease and do not have a damaged ureter. In 28 cases, Bricker had no mortality from constriction of this tube. His patients have gone into the second and almost the third year without any complications, except those who died of their original disease. The rest of them are doing well.

DR. A. N. ARNESON.—Some of Bricker's early patients had obstruction but not the recent ones. The earliest are now about four years postoperative.

DR. TE LINDE.—It is one thing to perform implantation in the presence of the normal urinary tract and quite another in the abnormal one. Dr. Everett has done some work on that.

DR. EVERETT.—I presented a paper before this Society in 1939 on the effect of radiation on the urinary tract. In that I attempted to show the prognostic value of preirradiation urologic study. In the cases classified as Stage III carcinoma, there was a difference between those that showed dilatation of the ureter in the pelvis before the institution of treatment and those that did not show dilatation. All those that showed dilatation of the urinary tract before, failed to respond to treatment and died; 75 per cent who did not show dilatation were well at the time of the report. I do not believe that in 1939 we were quite as certain of our staging of carcinomas as we are now. According to the International Classification of Stage III carcinomas, invading the parametrium and extending to the lateral pelvic wall, it appears that the ureters woud be bound to be obstructed.

DR. KARL H. MARTZLOFF.—I would like to ask Dr. Schmitz about resorption from the artificial bladder. I think he knows Dr. Bricker's results in that regard.

DR. SCHMITZ.—Quoting from his report, Dr. Bricker said: "Our approach to the problem has been to provide an intra-abdominal receptacle which would serve as a reservoir for urine. Use of the terminal ileum and cecum has been satisfactory, except that we have not been successful in making them truly continent. Therefore, we have turned to the Rutzen bag to solve this problem. The single stoma is put in a convenient location for this bag. . . . There is rapid emptying of the bag. The ileum is ideally situated to receive the cut ends of the ureter and the procedure is relatively easy. There has been no incidence of breakdown of anastomosis with urinary fistula. Postoperative azotemia is not a problem."

DR. MARTZLOFF.—I think this group should know that Dr. Gilchrist has an incidence of hydronephrosis, hydroureter, and pyelonephritis much the same as that following ureterosigmoidal anastomosis. Dr. Bricker's observations are simply astonishing. He has a small incidence of primary pyelonephritis, and an incidence of hydronephrosis and hydroureter which over a period of months and years almost completely disappears so that the Bricker technique offers a very favorable outlook for the life of the patient.

DR. MEIGS.—I would like to say something about the method that Dr. Langdon Parsons has been using; I am not sure but that it has great merit. He does a wet colostomy and he does a direct anastomosis, but he then does a transverse colostomy. He leaves a short sigmoidal loop for his wet colostomy. He thinks this has been of great help to him; he thinks there is less evidence of absorption and hyperchloremia, and he is convinced that this is a good way to do it. Is it not true that those patients do better who do not have a chance to accumulate large amounts of urine in the bowel? If you do a colostomy and an anastomosis and then a transverse colostomy which has an open end, there is no collection of urine; it drains all the time. That is much easier than doing a Bricker or Gilchrist operation.

DR. SCOTT.—I quite agree that frequent emptying of rapid run-off is important. Frequently following conventional ureterosigmoidostomy, the patient comes in with hyperchloremia and is treated by inlying catheter.

DR. MEIGS.—It is entirely different if you have a transverse colostomy. The patient does not have much absorption because it is running all the time.

DR. EVERETT.—This goes back to Dr. Taylor's question. Five of Dr. Wharton's cases were included in my series and some were nonmalignant.

As for the pouch operation, there is one factor that no one has mentioned. The pouch eliminates the presence of infected fecal material in the reservoir in which the urine is going to drain. Regardless of that, if the technique results in partial obstruction producing urinary stasis, which the Coffey techniques tend to do, sooner or later the patient will get a renal infection. This happens with obstruction even if the ureters are still draining into the bladder. So the aim of the technique should be to prevent obstruction at the point of anastomosis. The disadvantage of the Coffey technique is that a segment of ureter hangs over in the bowel and undergoes necrosis. The disadvantage of the direct method alone is that it is not tight enough and there is reflux of gas and fecal material back into the kidney and sometimes the anastomosis pulls apart. The Leadbetter technique makes an incision right down to the mucosa so there is no resistance from within. He makes an opening at the lower end and does a direct anastomosis and sutures the bowel over the top, which reinforces the anastomosis so it is not so likely to pull apart. He reports excellent results but it is too early to evaluate yet.

I would like to ask Dr. Scott about cortisone. In going over the literature, I came across two articles on the subject of preventing scarring and stenosis by the use of cortisone postoperatively.

DR. SCOTT.—That was reported by Dr. Roger Baker while at the University of Chicago, and a second report of his has just come from Washington, D. C. No one else has followed up this work, to my knowledge, so it remains virtually untried. It was a very nice piece of experimental work, and showed evidence of less stenosis at the site of anastomosis if cortisone were given.

DR. ARNESON.—I wish to ask about the disposition of a situation in which we might assume hopeless carcinoma existed, with invasion of the bladder and ulceration of the bladder but no leakage of urine, assuming also infection of the bladder with much pain. Removal of the bladder is inadvisable. The urinary stream was diverted and the bladder became almost a cesspool. Would this operation be done in such a situation when the bladder was invaded? Should it be done as a palliative measure for relief of pain?

DR. TE LINDE.—Do you think the pouch operation should ever be done for relief of symptoms when carcinoma exists?

DR. SCHMITZ.—I mentioned one patient in whom the pouch operation was done and at the time disease was found in the glands above the crest of the ilium and, therefore, no further attempt was made to do anything for her. She is very comfortable now. The urinary stream was diverted and she has very little discomfort. I think the answer depends upon the probable length of life of the patient. If you can give her six months of comfort, then I think it is worth while, especially if you choose the Bricker pouch procedure. I think with Cordonnier's method of approximation and the instruction of patients to keep that bag empty, they are having fewer urinary difficulties. In the beginning, Gilchrist instructed his patients to go four hours after the anastomosis, but some strictures with much upper urinary tract damage resulted. That can be alleviated by present methods, but I am convinced that that is too formidable a procedure to get continence and I do not know that continence is a desirable thing. I think open loops with continuous flushing are more desirable. As for Dr. Arneson's question, that depends upon the extension of the life of the patient. If you can give her six months of comfort, it is justified.

DR. EVERETT.—That was exactly what was done in 12 of our patients. The anastomosis was done purely to relieve intolerable symptoms in the presence of malignancy.

Two of those patients lived for more than a year; the others died in less than a year but we never expected them to get well. What does it matter whether these patients with hopeless malignancy die of renal infection or carcinoma? I think in such cases a technique simpler than the pouch procedure would be indicated. They are really doomed when the operation is done.

DR. MEIGS.—But you do get hydroureters following a Bricker operation, and I can illustrate that by these slides. Of course, you also get difficulties following any anastomosis but after a while they get much better.

DR. SCOTT.—One point in the Bricker operation is that the defect in the fascia has to be adequate to permit the bowel to get through. If stricture develops behind this, you get increased absorption.

DR. R. GORDON DOUGLAS.—The panel members seem to be opposed to cutaneous transplantation, but what is advised when the condition is unilateral?

DR. SCHMITZ.—The unilateral skin ureterostomy would be preferable if one side functions well. Too often, however, when we get complete obstruction, we whip out one ureter, hoping to establish function. We get excretion but we do not get function, and later on we sacrifice that kidney. If the opposite side is functioning well, skin ureterostomy on the opposite side is wise.

DR. SCOTT.—I am not opposed to cutaneous ureterostomy.

DR. ARNESON.—I do not believe I made my question clear. Assume we have a patient with carcinoma invading the bladder, with pain; the pain becomes more intense; fistula forms and the pain subsides. If there is no fistula, you divert the stream, but in my patient there was no benefit from diverting the urinary stream, at least as far as the pain was concerned.

DR. EVERETT.—I am not too sure about the answer to that. Many of these patients die very early, and some of them die within three months. My impression is that they were relieved of their intolerable pain and certainly of their extreme frequency.

DR. WHARTON.—I think we are all agreed that preoperative chemotherapy is good. Have you used any routine postoperative urinary antiseptics to prevent infection?

DR. SCHMITZ.—We have to maintain chemotherapy for some time after operation, but as soon as the patient is afebrile you must get her off antibiotics and on other preparations. I do not think it will be effective to continue it indefinitely. We have lost a number of patients who lived in other parts of the country who, when they began to have fever and pain, were not put on urinary antiseptics immediately; as a result, they had overpowering infection and died of kidney disease. I think it is important to instruct the patient that when she has fever or lumbar pain she should take antibiotics, and we supply them with these preparations when they go home.

DR. MEIGS.—I would agree to that.

DR. EVERETT.—I would agree too. We usually treat these patients preoperatively for five days with sulfasuxidine and then postoperatively with antibiotics. Honestly, however, in reviewing these cases which extend over a long period of time, I could not say that there was less infection since the availability of these newer drugs than there was before.

DR. SCOTT.—We should emphasize the value of mechanical cleansing of the bowel preliminary to these operative procedures. That is extremely important.

DR. TE LINDE.—We did not, of course, expect to have the last word on this subject, but we have had a healthy discussion and I want to thank the panel members for their part in it.

PELVIC EXAMINATION OF THE PREADOLESCENT AND ADOLESCENT GIRL*

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I HAD considerable difficulty in choosing a title for this presentation. The definition of "adolescence" according to Webster's Dictionary is, "The state or process of growing up from childhood to manhood or womanhood." I believe that almost everyone automatically thinks of the growing female as a child until puberty is established and as an adolescent girl until she is ready to assume the responsibilities of marriage, usually between the ages of 17 to 22 or 24 years.

Certainly the growing-up period is characterized by a rapidly developing series of anatomical changes, with their attendant functional and psychological phenomena which make this one of the most difficult and important epochs in a woman's life. The normality of this development will largely determine the future of her reproductive, sexual, and social being. Accurate medical and lay assistance during this critical period should offer one of the most fruitful and satisfying fields of preventive medicine left for us today. Many wide gaps in our scientific knowledge of this important phase of the individual's development remain to be explored. The timing and methods of imparting this knowledge to these eager youngsters is still uncertain and too frequently based, as is our scientific knowledge, on biased uncritical attitudes of thought. The mothers of these growing girls need and are asking for our best help in educating and protecting their daughters. I believe we should accept this educational and medical challenge rather than avoid it on the basis of the so-called intact, inviolate hymen, and the fanciful stories of the birds and the bees.

Due credit should be given to the Academy of Pediatrics for their early recognition of the need for medical supervision of children between the ages of 12 and 18 years. Many pediatricians have extended their care to cover this period. It is quite evident in our locality, however, that they have not asked for, or perhaps received, the needed cooperation of the gynecologist, as has been suggested by such pioneers as Goodrich Schauffler[1] in his monograph on pediatric gynecology. The triad of an educated mother, the pediatrician, and the gynecologist should spearhead this medical advance during these formative years of the girl's life. Further advances in the detection of early pelvic cancer will probably not occur until we educate our young

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women as to the ease and necessity of routine pelvic examination before the sex inhibitions become so fixed. Patient delay has not been appreciably shortened by our various extensive programs of lay education.[2, 3]

This report covers some of the details concerning the pelvic examinations and gynecological treatments suggested or carried out in 1,321 patients (Table I). Two hundred of these 1,321 patients were seen in the office as private patients between the years 1936 and 1953, inclusive. Their ages ranged from 3 to 17 years. The remainder of these patients, 1,121, were candidates for and accepted students in our School of Nursing at Presbyterian Hospital, Chicago. Of this group 1,209 were 17 to 22 years of age and 112 were over 23 years. From the group of nurses (1,121), only 20 had been or were married. The remaining 1,101 were presumably virgins.

TABLE I. TOTAL NUMBER OF INDIVIDUALS EXAMINED

	NURSES	PRIVATE PATIENTS
Presumably virgin nurses (ages 17-22 years)	989	
Unmarried nurses (23 or over)	112	
Married nurses	20	
Private patients (ages 3-17 years)		200
Total nurses	1,121	
Total patients		1,321

Due to the firm objections of the medical and nursing health supervisors routine pelvic examinations of the nursing students could not be undertaken until 1946. Fifteen years of effort were required to overcome these objections. During these last 8 years only 2 nurses have refused examination, and one of these requested examination one week later. In the beginning all examinations were done by the author. More recently we have allowed the girls to choose their examiner from the members of the Gynecological Staff, especially for their yearly checkup, which is now required.* These entrance and routine yearly gynecological examinations have for the last four years been extended to include all the female employees and staff nurses in the hospital. Worth-while rewards from rejection or improvement in service have resulted.

Most of the younger private patients were examined in the knee-chest position with the Kelly cystoscope. The approach to the complete pelvic examination was gradual, unless the need was acute. This was begun by recto-abdominal palpation and, when the confidence of the patient was secured, rectovaginal examination was done before the average age for the onset of menstruation. The nurses were examined in the usual dorsal position.

The physical findings in the nursing group were normal to rectovaginal and visual examination in 634 instances. Some type of abnormality in the physiology or anatomy of the sex or glandular systems was recorded in the

*The major portion of the routine entrance pelvic and yearly examinations during the last four years have been performed by Dr. C. C. Draa and Dr. H. C. Baum. We are grateful to them and the remainder of the Gynecological Staff for allowing us to use their recorded observations. We are also grateful to the Nursing Health Service, and especially to Miss Clarrisse Galloway, Miss Ruth Salstrom, and Mrs. Margaret Blaney for recording and compiling these observations.

remaining 487. These abnormalities ran the gamut from distressing hirsutism, through chronic cystic mastitis to such common pelvic conditions as vaginitis, cervical cysts and erosions, infantile uteri, retroversions, ovarian cysts and endometriosis. These abnormalities will be included in the following tables.

In 98 of these young women the hymenal ring was small or abnormal enough to suggest premarital stretching or incision either as a prophylactic measure for drainage or as a part of the surgical procedures of cervical cautery or dilatation. A few additional members of preceding classes or outside nurses who requested examination were similarly treated but not included in this report (Table II).

TABLE II. TREATMENT OF HYMEN AND CERVIX

Dilatation hymen	41
Incision hymen	12
Hymenal dilatation for cautery or dilatation of cervix	45
Cautery cervix	142

The average age of onset of the menstrual period in this group was 12.6 years. The average duration of flow was 5.2 days and the average requirement of menstrual pads was 13.1. Forty-five individuals used tampons. From this latter group three lost tampons were recovered, one that had remained in the vagina for a period of at least three months. Several others with uncomfortable or even blood-tinged vaginal discharges were relieved when the use of tampons was discontinued. We have suggested to this large group of young women that they use tampons only on rare occasions. We do not believe that the dilatation of the hymenal ring by insertion of a tampon in this small number of patients would materially affect the statistical evidence as to the patency of the normal introitus in the virgin. The wide use of this type of menstrual protection today by teen-aged girls, as well as the function of menstruation itself, should rid us for all time of the old conception of the intact hymen acting as a barrier to adequate pelvic examination. The average interval between menstrual periods given by these young women was 28.4 days, only 88 were astute enough to record the normal irregularities. A previous study of 1,522 menstrual intervals in the first 110 of these girls revealed variations from 17 to 40 days.

Approximately two-thirds (729) of these girls menstruated normally. Three hundred sixty-seven (32.7 per cent) gave histories of various complications ranging from primary dysmenorrhea to severe menorrhagia and metrorrhagia. Careful individualized gynecological supervision instead of self-diagnosis and medication have done much to correct these abnormalities which so definitely interfere with the health and efficiency of these important young women. A few individuals had more than one menstrual complication. Table III lists these abnormalities.

TABLE III. MENSTRUAL ABNORMALITIES

Dysmenorrhea	309
Amenorrhea	22
Menorrhagia	28
Metrorrhagia	5
Oligomenorrhea	2
Severe menstrual migraine	1
Total	367

In the 22 patients with amenorrhea early treatment should have an important bearing on future fertility. Only 85 of these girls were under the care of a physician for menstrual abnormalities when the preliminary entrance examination was done.

An interesting pilot study of dysmenorrhea conducted by the Nursing Health Service from 1949 through the completion of training in 1952 suggests the importance of increasing tension and responsibility in essential dysmenorrhea. Seventy-two girls complained of cramps during the first year, 120 during the second, and 443 during the third or senior year. During 1949, 6 nurses were off duty for a total of 19 days with pain; during 1952, 106 nurses lost 109½ days; a total of approximately 265½ days were lost by the 309 patients with dysmenorrhea. The nursing supervisors and we are convinced that this time loss would have been greatly increased without the benefit of the various treatments which were advised. The most outstanding increase in the incidence of dysmenorrhea occurred during the period of training in the psychiatric division. The most outstanding therapeutic results that we obtained were noted to be by changes in basic nutrition and the supervised use of thyroid.

The basal metabolism was checked when clinical evidence of aberrations of function was present (Table IV). These symptoms consisted of unusual dryness of the hair or skin, friability of the nails, bradycardia, tachycardia, abnormal body weight, fatigue, or menstrual dysfunctions. Realizing the inaccuracies of the basal metabolism determination, it was used only as confirmatory evidence. Clinical impressions and frequently a therapeutic trial with thyroid extract usually in small doses given under close supervision, commonly gave satisfactory clinical improvement when the basal rate was normal or occasionally even above normal. Hormones of other types were rarely prescribed for these young women, except in the occasional case of amenorrhea or oligomenorrhea.

TABLE IV. BASAL METABOLISM

	NURSES	PRIVATE
Nurses not checked	581	
Nurses checked one or more times	540	
Normal reading (-10 to +10)	228	34
Abnormal	312	24
Thyroid prescribed	164	49

Clinical vaginitis was present in 73 individuals. Seventeen of these cases were caused by Trichomonas, 26 by Monilia, and 30 were listed as nonspecific. The low incidence of vaginal infection in this group of virginal girls would tend to corroborate Trussell's[4] statement that specific infection of the vagina is largely associated with sex experiences (Table V).

TABLE V. VAGINITIS DISCOVERED AND TREATED

	NURSES	PRIVATE
Trichomonas	16	1
Monilia	13	13
Nonspecific	28	2

A review of the previous surgical histories of this group of adolescent girls can leave no question as to the need of competent medical supervision during this period of life. Three hundred seven had been operated upon before they applied for nurse's training. Of this group 13 operations were performed on the ovaries and 11 on other pelvic organs. We believe that with adequate

gynecological consultation the number of 84 appendectomies could have been materially reduced. The history of operation suggested that in only two of these patients true ovarian tumors were present.

The pelvic surgery performed on the nursing group during their period of training reveals the importance of abnormalities in this age group (Table VI). The cure of the one malignancy and possibly two is adequate reward for the effort expended during the entire study period. We believe that the education imparted to these individuals will save many of them from death due to pelvic malignancy in the future. We hope that they will accordingly act as ambassador of health to the patients they will attend in future years, and perchance will encourage their daughters to do likewise. All operations for endometriosis were conservative and we believe will help to conserve fertility until the patients are married. Our attitude toward the hymenal opening that is too tight to admit of routine pelvic examination is that simple dilatation, or, when it is malformed, incision, will decrease initial dyspareunia and frigidity and unhappy sexual adjustments. Many nurses who have graduated and are married have verified this attitude. Cauterizations of the cervix were usually done for increased vaginal discharge or when the erosions were symptomless but large in size (Table VII). The operation for pilonidal cyst and the one for hemorrhoids were done by the General Surgical Service in conjunction with necessary gynecological procedures. Nine nurses with endometriosis were operated upon, 4 through the posterior cul-de-sac. The lesion was either excised or cauterized through the posterior colpotomy incision. Twelve additional diagnoses of probable endometriosis were made. Two of the nurses who were advised to have operations but who refused have come to surgery since graduation (Table VIII). These were in the group with suspected endometriosis and an increase in symptoms indicated investigation. The remainder are routinely examined at six-month intervals. No appreciable advance in the endometriosis has been apparent in the remaining patients.

TABLE VI. SUMMARY OF OPERATIVE PROCEDURES

OPERATION	NO. OF CASES	NURSES			PRIVATE
		LAPOROTOMY	COLPOTOMY	COMBINED	
Endometriosis	8	2	5	1	
Dermoids (one portion benign teratoma)	2		1	1	
Teratomas (1 papillary cystadenoma?)	3	1		1	1
Serous cystomas	2		2		
Twisted hydatid cyst and appendix fecalith	1			1	
Bilateral cystic ovaries	1	1			
Persistent corpus luteum, severe dysmenorrhea (9 months)	1			1	
Webster round ligament, severe dysmenorrhea	2	2			
Appendix	1	1			
Freeing postappendiceal adhesions to abdominal wall and ovary	1	1			
Exploratory colpotomy, nothing found except movable retroversion	1			1	
Artificial vagina constructed	1				1
Total	24				

Examination of the smaller but important group examined as private patients reveals to us several interesting facts. By far the greatest percentage of the youngest patients were brought to the office either for disease or

routine examination by the mother. Some of them were referred by other intelligent or educated patients. Few were referred by doctors even for disease (Tables IX and X). Generally these patients were referred for acute discharge with irritation, attempted rape, or because they were bleeding abnormally (Tables XI and XII). No doctor's daughter who came for routine pelvic checkup is to be found in this list.

TABLE VII. MISCELLANEOUS PROCEDURES

Dilatation and curettage	45
Hymen dilated	41
Hymen incised	12
Cautery of cervix	142
Posterior colpotomy	11
Incomplete abortion	1
Removal vaginal cyst	1
Hemorrhoidectomy	1
Pilonidal cyst	1
Total	255

TABLE VIII. SURGERY ADVISED AND REFUSED

	NURSES	PRIVATE
Colpotomy	3	
Laparotomy for ovarian cyst	1	
Hymenotomy	2	
Dilatation	2	
Cauterization	3	
Perineal rectal fistula		1

TABLE IX. PATIENTS UNDER 18 YEARS OF AGE SEEN IN OFFICE, 1936-1953

Number of patients	200
Visits	600
Referred by parents	104
Referred by doctors	62
Referred by friends	34

TABLE X. PATIENTS UNDER 18 YEARS OF AGE SEEN IN OFFICE, 1936-1953

AGE	NUMBER OF PATIENTS
3 years	3
4	2
5	1
6	1
7	5
8	9
9	4
10	6
11	12
12	14
13	20
14	21
15	31
16	30
17	41

The large number of Monilia infections is noteworthy, as is the one case of Trichomonas vaginitis (See Table V). The one patient without a vagina was examined at the age of 12 years. No other office calls were made until she developed abdominal pain following hormone injections by the family physi-

TABLE XI. PATIENTS UNDER 18 YEARS OF AGE SEEN IN OFFICE, 1936-1953
COMPLAINTS

Gynecological.—	
Amenorrhea	12
Dysmenorrhea	36
Menorrhagia	24
Very irregular periods	21
Spotting between periods	8
Redness, irritation of vulva, discharge	12
Vaginal bleeding (8 years)	1
No vagina	1
Congenital defects (perineal rectal fistula)	1
Rape	1
Pregnancy	9
General.—	
Routine checkups	26
Urinary symptoms	7
Enuresis	3
Abdominal pain	7
Backache	2
Headaches	9
Fatigue, irritability, nervousness	1

TABLE XII. PATIENTS UNDER 18 YEARS OF AGE SEEN IN OFFICE, 1936-1953
FINDINGS

Adhesive vaginitis	4
Cervical erosions	7
Development—Male hair distribution	4
Marked development of vulva (12 years)	1
Hypertrophied lip over clitoris	2
Hymen tight—8, cribriform 1	9
Foreign bodies in vagina	2
Mass in cul-de-sac	1
Mental defective (request for sterilization)	1
Uterus, small	5
enlarged 5 times	1
Absence of vagina	1
Teratoma of ovary	1
Endometriosis (16 years)	1
Breasts—Lumps	5
No development	2
Irregular development	1
Albumin	7
Glycosuria	3

TABLE XIII. PATIENTS UNDER 18 YEARS OF AGE SEEN IN OFFICE, 1936-1953

Weights

Normal (6 pounds under or over)	62
Over	58
Under	43
Unrecorded (early years)	37

Menstrual History

AGE	NO. OF PATIENTS	DAYS OF FLOW	NO.
9	1	1	2
10	5	2	3
11	30	3	7
12	43	4	20
13	35	5	37
14	17	6	19
15	6	7	21
		More than 7	11

cian in an endeavor to start menstruation at 17 years of age and preparatory to marriage. This patient has been happily married for two years following the operation for making an artificial vagina. Three months ago a baby was procured for them for adoption.

A slowly increasing number of preadolescent girls are appearing at the office each year. Early correction of abnormal weight (Table XIII), thyroid dysfunction, and pelvic abnormalities should reduce difficulties in the mature girl. We agree with Schauffer when he says "extended experience has clearly proved that no serious remote effect occurs."

Conclusions

1. We believe that the individual education each one of these young women has received during the course of this health program has fully justified the effort expended.

2. The early detection and cure of one malignant tumor of the ovary and possibly a second one are alone ample justification for this statement.

3. We hope that none of these young women will come to marriage with gross pelvic lesions.

4. We have endeavored to demonstrate to these developing girls the ease and advisability of routine pelvic as well as general physical examinations. Many of them will undoubtedly impart this information to their daughters and women patients to whom they minister. Their future gynecological therapy should therefore be more accurate and satisfactory.

5. It is our impression that a closer doctor-patient relationship has been developed during these examinations. Neither we nor our psychiatrists have observed any undesirable effect.

6. It is our opinion that this program has contributed many tangible and intangible factors to the health and increased efficiency of this most important group of potential mothers and teachers.

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Discussion

DR. FRANK R. LOCK, Winston-Salem, N. C.—Ignorance, superstition, and numerous misconceptions on the part of the public, combined with the medical profession's overemphasis of the psychic implications of pelvic examination in preadolescent and adolescent girls, have resulted in a tendency to disregard their gynecologic problems. Our literature on this subject is poor and lacks detail, except for a few specific problems which have interested individual authors. Moreover, physicians in the various specialities concerned have cooperated poorly in the study of this group of patients. Dr. Allen has pointed out the failure to assign definite medical responsibility for children between 12 and 18 years of age, and has noted with approval the position taken by the Academy of Pediatrics.

Although I do not feel qualified to discuss Dr. Allen's paper, since I lack experience in routine pelvic examination of healthy young women, I am completely in accord with his concept and approve the principle of examining these patients. Pelvic examination

permits the child to become oriented to medical supervision, and dissolves inhibitions which have perpetuated the consistent neglect of this group. Further, it encourages the practice of obtaining medical aid promptly for gynecologic disorders which may arise in the future.

My experience with the examination of preadolescent and adolescent girls has been limited to those referred for various definite complaints. The fact that an adequate pelvic examination can be performed without difficulty or discomfort on those who are ill indicates that normal adolescents could be examined with even greater ease.

In the vast majority of cases, the cooperation of these girls is easily gained by a little patience and explanation of the examination to be performed. Certainly little, if any, psychic trauma should result from pelvic examination when the patient's confidence has been gained and when it is performed with gentleness. The mother is discouraged from accompanying the patient to the examining room. Occasionally two or more visits are required to establish sufficient rapport for the patient to consent willingly to pelvic examination. In my experience it has been necessary to give anesthesia in only three cases, and only one mother has refused to permit pelvic examination of her child.

Dr. Allen has properly emphasized the high incidence of functional gynecologic abnormalities in presumably healthy young women. Further, he has found that the use of simple educational and medical measures will relieve the majority of such complaints. The fact that a number of organic abnormalities, including two malignant lesions of the ovary, were discovered in his patients emphasizes the importance of gynecologic study of girls in this age group.

Two hundred fifty-four private patients under 20 years of age have been referred to me for obstetric and gynecologic complaints. A review of their records demonstrates the diverse diseases found among this age group in our area (Table I). Organic gynecologic disease involving the pelvis or reproductive system was present in 52 patients, functional gynecologic problems in 142, pregnancy and its complications in 52. Eight of the 254 patients had urologic rather than gynecologic diseases.

TABLE I. FINDINGS IN 254 OFFICE PATIENTS UNDER 20 YEARS OF AGE

	AGE (YEARS)				
	0-5	6-10	11-15	16-20	TOTAL
Organic Pathology.—					
Congenital anomalies					12
Absence of vagina and uterus	1			4	
Absence of vagina with vestigial uterus				2	
Bicornuate uterus				3	
Intersexual		1		1	
Adherent labia	4				4
Neoplasms					4
Malignant	1				
Benign				3	
Salpingitis			1	4	5
Vaginitis and cervicitis	2	4	2	3	11
Miscellaneous (breast and obesity)					16
Total					52
Functional Disease.—					
Bleeding			9	23	32
Puberty praecox	2	2			4
Oligo- and amenorrhea				12	12
Severe dysmenorrhea		1	5	38	44
Psychosomatic disease		2	7	21	30
Premarital				6	6
Miscellaneous					14
Total					142
Normal pregnancy				50	50
Abortion				2	2
Urologic disease			1	7	8

Problems normally expected in mature women are often present in this age group. Fifty of the 254 patients I have seen were referred for ordinary obstetric care. In addition, 16 patients came for premarital examination or for advice concerning sexual maladjustment in marriage. Four neoplasms, one malignant, were encountered.

Two of this group of 254 patients, and one older patient, were sex intergrades. All had had inaccurate diagnoses at birth, and their sex had been improperly registered. Congenital anomalies, present in 15 patients, had been recognized in only one before the age of 16. These 18 cases emphasize the importance of careful genital examination of the newborn.

Significant menstrual dysfunction is most common after the age of 16. Puberty praecox, however, was observed in one patient at 6 months and in another at 2 years of age. Functional amenorrhea is seldom significant if signs of orderly secondary sexual development are present. Of incidental interest is the presence of disabling functional dysmenorrhea in a patient 8 years old, and of cyclic organic pain in two patients without vaginas who had vestigial uterine horns.

Like Dr. Allen, we have used simple medical measures rather than operative procedures in the treatment of functional menstrual problems. Dilatation and curettage was used in 7 of 32 patients with abnormal bleeding, but was not recommended in other conditions.

DR. RONALD R. GREENE, Chicago, Ill.—Apparently in not very many hospitals is it a routine to perform pelvic examination on student nurses on their admission to training. At Wesley Memorial Hospital in Chicago it is a routine, and I have been the examiner for the last four years. About 460 nurses have been examined during this period. I am of the opinion that the "conditioned reflex" against these examinations is mostly in the minds of the doctors and not in the minds of these young girls. I have found no serious pathology in this group of girls. There were some with very minute hymens which needed dilatation, which was usually done in my office. There were some vaginitis and cervicitis. I am sure that this is a valuable experience to the girls, and I am sure it helped some of them get rid of a condition that might have been a serious inhibition later in life. I think Dr. Allen's remarks about the value of examining these girls cannot be overemphasized.

DR. ALLEN (Closing).—I wish to tell a little story in line with what Dr. Greene has said.

I presented this subject at a medical meeting in Arizona at which a psychiatrist was present and I asked him to discuss it from the psychiatric angle. He said that he would but he avoided it. The next day in his paper he talked about the definitive surgical measures we could introduce into our specialty but he pointed out that psychiatrists had to depend entirely upon patient-doctor relationship and that the men in his specialty acted as a crutch for the patient. When he had finished the chairman asked for discussion, and I again asked him if he would speak on the point of pelvic examination for adolescent girls from the psychiatric standpoint. He said: "We never do it at our school because our patients would call it sexual intercourse or sexual attack." The chairman asked me what I had to say to that and I said: "That has not been our experience and I will tell you a story about a mother who brought her two daughters into my office on the way to the dentist. One little girl was 11 years old and the other 6½. The younger child stood at my side when I took the history, and then I asked her, 'What about examining you?' And she said: 'Fine. What do I do?' I told her to get the nurse and when she was ready I would come in. When I came in she had taken off all her clothes, which the adult patient does not do. I examined her rectoabdominally and told her that was all there was to it. She hopped down on the step at the end of the table and said: 'Where are my pants, Doctor?' I said: 'Here they are and I'll help you put them on.' Then I said to the psychiatrist: 'You spoke about patient-doctor relationships. When you have a strange woman, stark naked, who asks you where her pants are and you help her put them on, I think that is the closest patient-doctor relationship there is.'"

PROGESTERONE TREATMENT OF ANOVULATORY BLEEDING*

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THE use of progesterone† in the management of anovulatory bleeding problems has been deprecated by some authors. In two recent textbooks, for example, statements are made to the effect that "to try to convert anovulatory into ovulatory cycles by the simple expedient of supplementary progesterone therapy is a rather fatuous ambition in the present state of our knowledge,"[1] and, "Progesterone is of little value in controlling excessive functional bleeding."[2] We have found the cyclic administration of progesterone to be an effective form of therapy, however. Not only does regular cyclic bleeding occur during the course of treatment, but spontaneous ovulatory cycles usually follow when therapy is discontinued except in women approaching the menopause.

Without attempting to review the conflicting literature on the subject or imply that the method of treatment to be described is based on a completely original concept, our experience with this type of therapy will be presented.

Rationale of Therapy

During anovulatory cycles the endometrium undergoes proliferation of varying degree depending on the length of time it has been subjected to estrogen stimulation before withdrawal bleeding occurs. In most cases the estrogenic effect has been sufficiently prolonged to produce a hyperplastic endometrium but bleeding may occur while the endometrium shows only moderate proliferation. The administration of a sufficiently large dose of progesterone will convert either the hyperplastic or proliferative endometrium to the secretory phase. Shedding of the converted endometrium follows in about four days. Therefore the irregular and prolonged bleedings associated with anovulatory cycles can readily be controlled by such therapy. In itself, this result is enough to justify the use of progesterone in the management of anovulatory bleeding problems. A more provocative concept is that the progesterone, in addition to being substitution therapy, also initiates a chain reaction which results in subsequent spontaneous ovulatory cycles. The experimental evidence to support such a concept will be briefly presented.

The exact hormonal stimulus which initiates ovulation in the human female is not well understood. The best evidence indicates that no one hormone is responsible. It is likely that ovulation occurs when an optimal ratio has been reached between the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). It is reasonable to assume that in anovulatory

*Presented by invitation at the Seventy-seventh Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 20, 21, and 22, 1954.

†The progesterone (Proluton) used in this study was supplied by the Schering Corporation.

cycles an imbalance between the secretion of FSH and LH exists. It is unlikely that either hormone is completely absent for it has been well established experimentally that both FSH and LH are necessary for the production of estrogen. In anovulatory cycles the estrogen effect on the endometrium is readily apparent. Until more precise and specific methods of analysis for the gonadotropins are available, the conditions necessary for ovulation cannot be further defined.

There is experimental evidence which indicates that progesterone can influence the secretion of gonadotropins. Ovulation has been induced experimentally in the chicken,[3] rat,[4] and rabbit[5] by the administration of a single dose of progesterone. Ovaries of rats in persistent estrus due to experimentally induced hypothalamic lesions show no corpora lutea. Following small doses of progesterone, large corpora lutea are formed.[6] These data indicate that progesterone may elicit the secretion of gonadotropin.

It is also possible that progesterone may exert a direct effect on the ovary. Such an effect could be in the direction of sensitizing the follicles so that they are able to respond with ovulation when properly stimulated by the gonadotropins. If progesterone plays a role in ovulation its presence prior to ovulation should be demonstrable. The fact that progesterone has been isolated from developing and preovulatory follicles in several ungulates[7] would lend support to such a hypothesis. The presence of a progestational substance (progesterone ?) in the blood of many species including the human prior to ovulation has been verified.[7, 8, 9] On the basis of these experimental data the progesterone treatment of anovulatory bleeding appears to be logical. Our clinical experience has convinced us of its value.

Method of Treatment

Although progesterone can be used effectively in all cases of anovulatory bleeding, the intent of therapy is different in the patients who are approaching the menopause. In the latter age group the treatment schedule is modified as indicated later. Between the menarche and 35 years of age the treatment is carried out in the following manner. A single dose of 25 to 50 mg. of progesterone is used. Although it was previously thought necessary to administer the progesterone in divided doses over several days, a single parenteral injection has been found to be just as effective. Recent results indicate that 25 mg. is probably as effective as 50 mg. About four days after the progesterone administration the endometrium will be shed. Regular cyclic bleeding can then be induced by the administration of the progesterone on the twenty-fourth day of succeeding cycles. If bleeding fails to follow in four days there are three possible explanations: (1) Ovulation has occurred recently, in which event bleeding will appear within fourteen days. The single injection of progesterone will have no effect on an endometrium already in the secretory phase. (2) The endometrial proliferation has not been sufficient to respond to progesterone stimulation. (3) Pregnancy has intervened.

If bleeding occurs as expected, the progesterone is repeated on the twenty-fourth day of the next cycle. This schedule is continued until there is evidence that ovulation is occurring spontaneously. This is indicated by failure of bleeding to follow the expected pattern. If bleeding occurs earlier or later than four days following the progesterone, therapy is withheld during the next cycle. Endometrial biopsy is obtained at the onset of the next bleeding. If biopsy indicates that ovulation has occurred, the patient is instructed to report only if bleeding fails to occur subsequently at the expected time. Recurrence of anovulatory cycles is usually heralded by a lengthened cycle. In this event, one injection of progesterone will usually be effective in initiating ovulatory cycles again. Should the lengthened cycle be due to an early pregnancy, the progesterone will have no harmful effect.

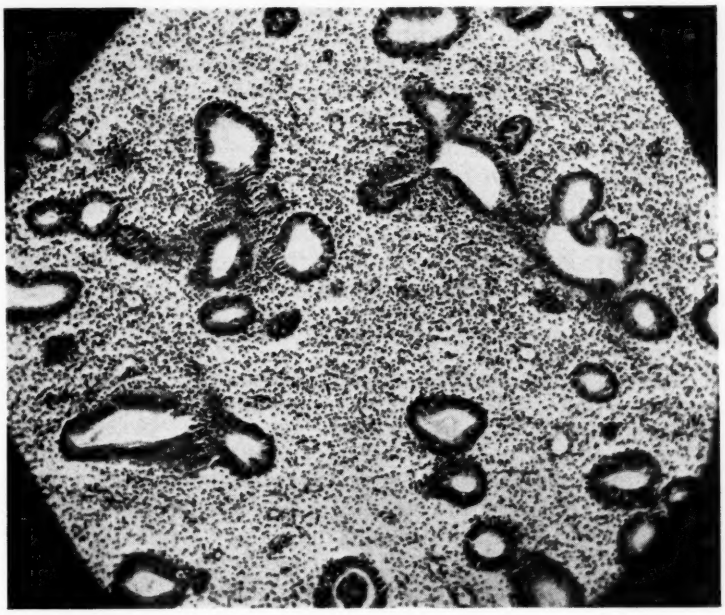

Fig. 1.—Endometrial biopsy on twenty-eighth day of anovulatory cycle in patient approaching the menopause.

When anovulatory bleeding occurs in women over the age of 35, it is usually an indication of failing ovarian function. Although sporadic ovulatory cycles may occur for several additional years, these are frequently interspersed with anovulatory cycles and prolonged bleeding episodes which may be exsanguinating. The purpose of the cyclic progesterone therapy in these patients is to avoid the profuse bleeding periods until ovarian production of estrogen ceases. This can be easily accomplished by the administration of 25 mg. of progesterone at approximately thirty-day intervals. By this time the endometrium, in the absence of ovulation, will show some degree of proliferation. (Fig. 1 is a section of endometrium obtained on the twenty-eighth day of an anovulatory cycle. On the same day 25 mg. of progesterone was given. Bleeding followed in four days.) Eventually there will be no response

to the progesterone administration. If bleeding fails to occur after three injections at monthly intervals it is assumed that the patient has entered the menopause. Sporadic recrudescence of ovarian activity may appear within the next year or two. Prompt administration of progesterone will ensure that any subsequent bleeding on this basis will be self-limited.

The alternatives to cyclic progesterone therapy in this age group are radiation castration or hysterectomy. Radiation castration is frequently followed by troublesome vasomotor menopausal symptoms. Hysterectomy is admittedly radical treatment for a benign condition which can be satisfactorily handled nonsurgically.

Clinical Results

The clinical history of patients with anovulatory bleeding is so typical that the diagnosis can be strongly suspected on the basis of history alone. Lack of regularity of the bleeding pattern and the absence of menstrual molimina are the two constant features. Although the problem is most often encountered in the pubertal girl and the woman entering the menopause, it also occurs during the intervening years. The diagnosis is made by examination of the endometrium at the onset of bleeding. At that time the endometrium will show either proliferation or hyperplasia. Evidence of progestational effect is absent. In the pubertal girl it may be permissible to make a presumptive diagnosis on the basis of history alone without resorting to curettage. If the response to therapy is not prompt, even in these cases curettage should be performed to rule out local causes of abnormal bleeding.

The clinical cases have been divided into three groups as follows:

1. Primary—no history of previously regular menstrual periods.
2. Secondary—under 35 years of age, previously regular menstrual periods.
3. Menopausal—over 35 years of age.

Table I summarizes the results of therapy in the cases falling into the primary category. The duration of the bleeding complaint ranged from four months to fourteen years. Spontaneous ovulatory cycles followed therapy in all cases except one. The 27-year-old patient with the fourteen-year history has had only one ovulatory cycle in four years of observation. A single monthly injection of progesterone, however, keeps her on a regular schedule and avoids the prolonged bleeding episodes which she otherwise experiences. (The last case listed had not ovulated spontaneously when the table was prepared but she has since had a spontaneous ovulatory cycle.) The time interval between the first progesterone injection and the first proved ovulatory cycle varied from one to six months. About half the patients experienced at least one recurrence. There was prompt resumption of ovulatory cycles in all these patients following one or two injections of progesterone.

Table II summarizes the results in the secondary group. The results are essentially the same as in the primary group. Two of the three patients in whom the treatment failed had been given intrauterine radium in what was described as a "substerilizing dose." The radium application produced short respites from bleeding following which the problem recurred. It is likely that the radium has produced ovarian damage to the extent that the ovaries cannot respond with ovulation even though the gonadotropin secretion is normal. The 33-year-old who has failed to ovulate probably belongs in the menopausal group. Although the percentage of recurrence is high, as in the primary group, a single injection of progesterone will usually be followed by ovulatory cycles.

TABLE I. PRIMARY (NO PREVIOUS REGULAR PERIODS)

AGE	DURATION BEFORE TREATMENT	FIRST OVULATION AFTER TREATMENT	RECURRENCE
17	3 years	4 months	1 in 8 years
18	2 years	3 months	0 in 5 years
17	4 years	4 months	2 in 2 years
16	2 years	6 months	2 in 5 years
20	9 years	3 months	0 in 3 years
18	6 years	2 months	0 in 3 months
16	1 year	3 months	0 in 3 months
22*	9 years	4 months	1 in 3 years
27	14 years	11 months	†
24	8 years	3 months	0 in 2 years
12	4 months	1 month	1 in 1½ years
11	6 months	1 month	0 in 6 months
16	3 years	0 in 6 months	

*Intrauterine radium six years previously.
†One spontaneous ovulatory cycle in four years.

TABLE II. SECONDARY (MENSES PREVIOUSLY REGULAR)

AGE	DURATION BEFORE TREATMENT	FIRST OVULATION AFTER TREATMENT	RECURRENCE
23	5 years	3 months	0 in 4 years
31	10 years	3 months	0 in 2½ years
18	3 years	6 months	2 in 6 years
28*	4 years	0 in 5 years	——
27†	6 years	0 in 1½ years	——
33	1 year	0 in 1 year	——
28	4 months	1 month	0 in 2½ years
29	4 months	1 month	1 in 2 years
26	2 months	2 months	0 in 2 months
20	10 months	1 month	1 in 3 years

*Intrauterine radium two years previously.
†Intrauterine radium three years previously.

Table III lists the menopausal patients. It will be noted that some of these patients have been under therapy over three years. All except one have had sporadic ovulatory cycles interspersed with the anovulatory cycles. When ovulatory cycles have occurred the progesterone has been omitted.

TABLE III. MENOPAUSAL

AGE	DURATION OF TREATMENT	SPONTANEOUS OVULATORY CYCLES
42	32 months	3 in 32 months
41	22 months	2 in 22 months
50	15 months	6 in 15 months
41	39 months	5 in 39 months
42	12 months	11 in 12 months
42	18 months	5 in 18 months
43	13 months	6 in 13 months
40	35 months	13 in 35 months
42	14 months	12 in 14 months
40	12 months	3 in 12 months
43	11 months	4 in 11 months
40	4 months	2 in 4 months
46	26 months	0 in 26 months
38	36 months	2 in 36 months
37	18 months	2 in 18 months
44	14 months	12 in 14 months

Comment

We are convinced of the clinical effectiveness of single-dose progesterone therapy in the management of anovulatory bleeding problems in all age groups. We believe that the therapy is more than substitutional in its effect. To prove this contention, it will be necessary for us to demonstrate that the administration of progesterone influences the pituitary production of gonadotropin. This requires a bioassay method sensitive enough to measure small changes in the production of FSH and LH, for we must assume that, even in anovulatory cycles, both hormones are being produced to some extent. A sensitive bioassay method recently developed in our laboratory allows us to measure small changes in the FSH level.[10] The method utilizes the known synergistic effect of FSH and chorionic gonadotropin (HCG) on the immature mouse ovary. A dose of HCG sufficiently large to produce a maximal luteinizing effect is administered. Any subsequent increase in ovarian weight following administration of the sample to be tested is assumed to be due to FSH. Preliminary observations on patients with anovulatory bleeding problems are encouraging but the studies have not progressed to the stage where we can reach any final conclusions. One patient who has failed to respond to therapy shows no increase in FSH production after the administration of progesterone; a second patient who responded to therapy showed a marked increase in the production of FSH following progesterone administration.

Conclusions

1. Anovulatory bleeding problems in any age group can be effectively managed by cyclic single-dose progesterone therapy.

2. In the absence of complicating factors such as prior radiation therapy, spontaneous ovulatory cycles can be expected to follow therapy in patients under 35 years of age.

3. Recurrence of anovulatory cycles is frequent but response to repeat treatment is prompt.

4. Cyclic progesterone therapy makes it possible to treat bleeding problems caused by menopausal hyperplasia satisfactorily without resorting to irradiation or surgery.

5. The FSH augmentation test should help to determine whether or not the administration of progesterone influences the output of FSH.

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Discussion

DR. ALLAN C. BARNES, Cleveland, Ohio.—In 1911, Leo Loeb, on the basis of valid and reproducible animal experiments, proposed that the function of the corpus luteum was to inhibit ovulation, a concept which influenced medical thinking for several decades. The large group of papers which appeared during the 1920's dealing with the ovarian effects of the injection of crude corpus luteum extracts all confirmed the fact that such materials delayed or aborted ovulation.

When, in 1929, Corner and Allen showed that the progestational changes in the rabbit endometrium were due to a specific substance, it still appeared that "progestin" aided nidation by (a) preparing the endometrium and (b) preventing subsequent ovulation. This seemed to be a logical and simple sequence of events. And when, in 1934, three groups of workers almost simultaneously isolated progesterone, it appeared that the therapeutic application of this steroid would be exceedingly limited—limited almost to the point of being nonexistent—the only candidates to receive it being that group of sterility patients who had ovulated but failed to form a functioning corpus luteum. For, if the patient's own ovary was not (endogenously) administering progesterone, in the majority of cases the likelihood was that she had not ovulated, and there was little sense in the exogenous administration of the hormone, either to prepare the endometrium for a nidation that could not occur, or to postpone ovulation in a woman who had not ovulated.

This apparent simplicity of progesterone—both with respect to its basic physiology and its therapeutic application—has disappeared under a deluge of fundamental scientific investigation and reports of clinical therapeutic trials. If, however, one reads these papers as a metaphysician rather than as a physician, one notes that actually only two new concepts have been added to the physiology of progesterone during these two decades. The first was the relation of this hormone to menstruation, achieving its best early expression in Dr. Corner's "Harvey Lecture" published in 1934. The second was the introduction of evidence that progesterone was not entirely an inhibitor of ovulation but might be an etiological agent in the ovulatory process, a concept we owe principally to the work of Everett and of Rothchild and Fraps.

The study which Dr. Holmstrom has presented today involves both of these concepts. Thus, on the one hand he concludes that the cyclic administration of progesterone makes it possible to regulate menstrual bleeding abnormalities satisfactorily. On the other hand, he concludes by implication that in the woman under 35—and, hence, the woman whose ovary represents a responsive end organ—the administration of progesterone can cause ovulation to occur.

The first of these conclusions, namely, that with the group of patients over the age of 35 displaying hyper- and polymenorrhea, the cyclic administration of progesterone represents a satisfactory form of therapy, is a conclusion that brooks very little argument. J. S. L. Browne, in 1938, reported the impact of intermittent progesterone on menstrual abnormalities; and Allbright, that same year, contributed the term "a medical D and C." The year 1942 saw the third of three papers by Zondek and co-workers, as well as the reports of Allen and Heckel and of Jones and Te Linde. Rakoff, in 1946, and Gray, before this Society in 1949, have also reported on progesterone-induced bleeding. While the dosages employed by these various workers cover a wide range, there is general agreement among them that in amenorrhea with evidence of some estrogenation, as well as in dysfunctional bleeding with endometrial hyperplasia, the intermittent administration of progesterone will impose a regularity of bleeding in a variable percentage of patients. This is not the only form of therapy which has been advocated, but it is a good one, and more physiologic than is, for example, testosterone for these women. One would piously hope, however, although Dr. Holmstrom does not say it, that all of the patients in this group would have a thorough dilatation and curettage rather than trust endometrial biopsy to rule out the presence of intrauterine pathology.

As all of us might agree with this first conclusion which Dr. Holmstrom establishes, I must immediately confess that personally I also agree with the second conclusion. Dr. Rothchild was the Director of our Endocrinology Laboratory and, impressed by his continuing studies on progesterone in human ovulation, I am inclined to suspect that ultimately it will be demonstrated that this steroid plays a direct or a permissive role in the etiology of human ovulation, as it does experimentally in the laboratory animal. That day is not yet, however, and, as Dr. Holmstrom points out, although the conclusion is possibly correct, the present work does not finally establish it.

The technique of FSH determination which Dr. Holmstrom and his group have sponsored is a good one. It has the disadvantages of all animal assays, but it does provide a weapon for following changes in gonadotropic excretion. It is to be hoped that, armed with this weapon, they will continue to explore this important field.

In any such continuation of these investigations, it would be pleasant if certain additions were made to the study. In the first place, it would be perhaps helpful if the diagnosis of ovulation vs. anovulation were certified with basal body temperature curves so that we might have continuing evidence of ovarian responsiveness rather than a single picture of the endometrial starting point. Careful studies on the thermogenic action of progesterone have indicated that the effect of a single administered dose of this steroid can be clearly differentiated from the sustained temperature rise of ovulation, and in the present study more precision could be given the diagnosis of ovarian response.

In the second place, women who fail to ovulate for a period of time may resume regular ovulation spontaneously. The frequency with which this occurs is not precisely known, although the longer the period of anovulation, the less likely, presumably, is the chance of spontaneous recovery. This leaves us, however, with another statistical imponderable which would suggest that, in a continuation study, half the patients receive the same injections of oil but with no progesterone in it, and I think we should all seriously contemplate some day an exhaustive investigation of the effect of 1 c.c. of intramuscular sesame oil in the common gynecologic disorders.

In Dr. Holmstrom's duration of therapy—one day—and his dosage—25 mg.—he has contributed a careful examination of a minimal standard. The follow-up on his patients is prolonged and good. His stated conclusions are valid, and his rationale challenging. This constitutes a valuable progress report in an important area of our present-day therapy. While results as good as this are probably not entirely coincidence, nevertheless if these results are to be attributed to the progesterone, one would hope (as is always true of clinical studies) that as the investigation continues, it will be possible to include untreated controls as well as patients treated with some of the other hormones advocated for these menstrual abnormalities.

DR. WILLARD ALLEN, St. Louis, Mo.—I had a patient who received estradiol benzoate for menopause. She received 1 c.c. per week and each cubic centimeter contained 1⅔ mg. of the hormone. This went on for some time, and then I decided to reduce the dose. The next week I gave her 1 c.c. of oil which could only be identified by carefully looking at the label. After two weeks the patient said: "What's wrong with those shots?" I submit that that is a control. I think in this kind of study the patient is her own control, which is a statement given in support of Dr. Holmstrom's work. We see these patients month after month and they have a menstrual picture which has lasted months or even years. In many cases we give a few doses of progesterone and something happens rather quickly. The intriguing thing is that, in many of them with chronic anovulatory behavior, there is appearance of ovulatory cycles very promptly after one short course of progesterone. The real problem is that of finding out what happens to the pituitary-gonadal balance as a result of progesterone.

Dr. Holmstrom has worked out a nice way of measuring FSH in the urine. With that new method it may become possible to find what does happen when progesterone is used. There are so many peculiar things that turn up sporadically that one wonders if progesterone may not actually induce ovulation occasionally. There is a very interesting

strain of rats in which the females stay in continuous estrus. In these rats the administration of a single dose of progesterone will cause the follicles to become nonfunctioning. Within five or six days the ovary is back again functioning as before. The intriguing thing about these animals is that if they are given progesterone continuously, they have spontaneous ovulatory cycles which will be fertile if the animal is mated. These are the best animal experiments I know of which tend to help our thinking in these problems. The easiest way to look at hyperplasia is to consider that the ovaries are producing estrogen continually in a noncyclic manner.

What about a single dose of progesterone? Some four or five years ago we were inducing withdrawal bleeding in elderly women with progesterone after priming with estrogen. If progesterone was given for ten days a nice progestational endometrium was produced with prompt withdrawal bleeding on cessation of injections. We reduced the progesterone injections to five days and every patient exhibited withdrawal bleeding. Next we reduced the period of treatment to one day and again they all had withdrawal bleeding. We were quite surprised to find that the single injection of 10 mg. or even 5 mg. usually led to withdrawal bleeding, which leads me to the conclusion that any endometrium suitably primed with estrogen, if given progesterone, has to break down, and that it does not require prolonged periods of exposure to progesterone. That may have some bearing on our interpretation of abnormal cycles. If a woman who had had a normal menstrual pattern suddenly begins to have cycles every two weeks, we assume that those cycles were anovulatory. Anovulatory behavior in most people's minds usually is interpreted as being a cycle without progesterone. It is just as easy to explain the two-week cycle by assuming that the follicular phase is terminated by a brief production of progesterone without ovulation having occurred. I think that with the techniques for measuring gonadotrophins worked out at the University of Utah it will be possible to go into a detailed study of these problems which we all see and on which we have very little information.

DR. HOLMSTROM (Closing) (By invitation).—I originally planned to say something about the FSH augmentation test which we have been applying to the study of patients who present anovulatory bleeding problems, but we do not have enough information from this study yet to draw any conclusions. We hope to demonstrate that the administration of progesterone influences the ouput of gonadotropins. Wih this test it should be possible to demonstrate small changes in the secretion of FSH. The test utilizes the known synergistic effect between chorionic gonadotropin and FSH. The test animals are first primed with HCG and the sample to be tested is administered. Any further increase in ovarian weight is due to FSH because the chorionic gonadotropin will mask any LH present in the specimen. The difficulty with previous assays has been to differentiate between LH and FSH effects. We hope that within the next year or so we will have some definite information to contribute on this point.

I think it is not wise to assume, on the basis of the history, that the patient has a functional bleeding complaint and particularly is this so in the menopausal age group. Perhaps in the very young patient—the girl of 12 or 13—the history is so typical that it might be permissible to assume that she is having anovulatory cycles and initiate treatment on the basis of a presumptive diagnosis.

It would be nice to have basal body temperature curves on these patients. Perhaps I do not have the respect for these curves that Dr. Barnes has. I have difficulty in evaluating them.

I agree entirely with the remarks about controls, but we are dealing with patients who have bleeding problems and it is hard for me to decide that this particular patient should be denied the very beneficial effects of progesterone for the purpose of proving that some other type of therapy is not as effective. The vast majority of patients have had years of treatment before they came to us. There are only a very few who have not run the gamut of therapy from thyroid extract on down, including all kinds of hormones. From that standpoint, I feel we have some degree of control on the basis of therapy they have previously had without permanent beneficial effect.

THE GYNECOLOGICAL ASPECTS OF ADRENAL HYPERPLASIA AND ALLIED DISORDERS*

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FEMALE pseudohermaphroditism due to congenital adrenal hyperplasia is well recognized by pediatricians and endocrinologists. Prior to the discovery by Wilkins and co-workers[1] that cortisone could successfully arrest the progress of virilization, treatment often consisted in unsuccessful resection of the adrenals and correction of the pseudohypospadias by urological surgeons. With the arrest of virilization and the induction of menstruation by cortisone, the gynecologist may now be called upon for plastic reconstruction of the external genitals.

The experience with cortisone in pseudohermaphroditism led Jones, Howard, and Langford[2] to try this agent in the therapy of a selected group of women with hirsutism, oligomenorrhea, and infertility. These women also proved to be benefited by this therapy and the relationship of this syndrome to female pseudohermaphroditism of adrenal origin naturally arises.

Further study has led us to believe that these syndromes are indeed closely related and could even be manifestations of a similar disease process, differing only in degree of severity and time of onset. The purpose of this paper is twofold: first, to consider congenital adrenal hyperplasia from the point of view of the gynecologist and, second, to consider its relationship to the syndrome of hirsutism, oligomenorrhea, and infertility. These purposes will be served by reviewing four groups of individuals who seem to have a related disease process of diminishing severity. The pathological changes in the adrenal, ovary, and urogenital-sinus derivatives will be discussed and, finally, the management of these patients from the gynecological point of view will be presented.

Clinical Classification

I. Female Pseudohermaphroditism Due to Congenital Adrenal Hyperplasia.—

Although, as early as 1866, Crecchio[3]† described in detail the history of an individual, Joseph Marzo, who lived as a man, but whose autopsy revealed adrenals as large as kidneys and with atrophic Müllerian derivatives and a vagina opening into the urethra, it has been only recently that female pseudohermaphroditism due to adrenal cortical hyperplaisa has been well recognized.

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†Otto (Otto, A. W.: Seltene Beobachtungen zur Anatomie, Physiologie und Pathologie gehörig, Breslau, 1816) is usually given priority for a description of a case of female pseudohermaphroditism with large adrenals. A careful reading of this reference fails to substantiate this.

Young,[4] for instance, in his classic book, "Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases," in 1937, described this syndrome under at least three separate headings.

The clinical and endocrine features are now familiar to pediatricians, and to Wilkins[5] in particular should credit go for clarifying the syndrome, occurring in genetic females and characterized by virilization with hirsutism, an

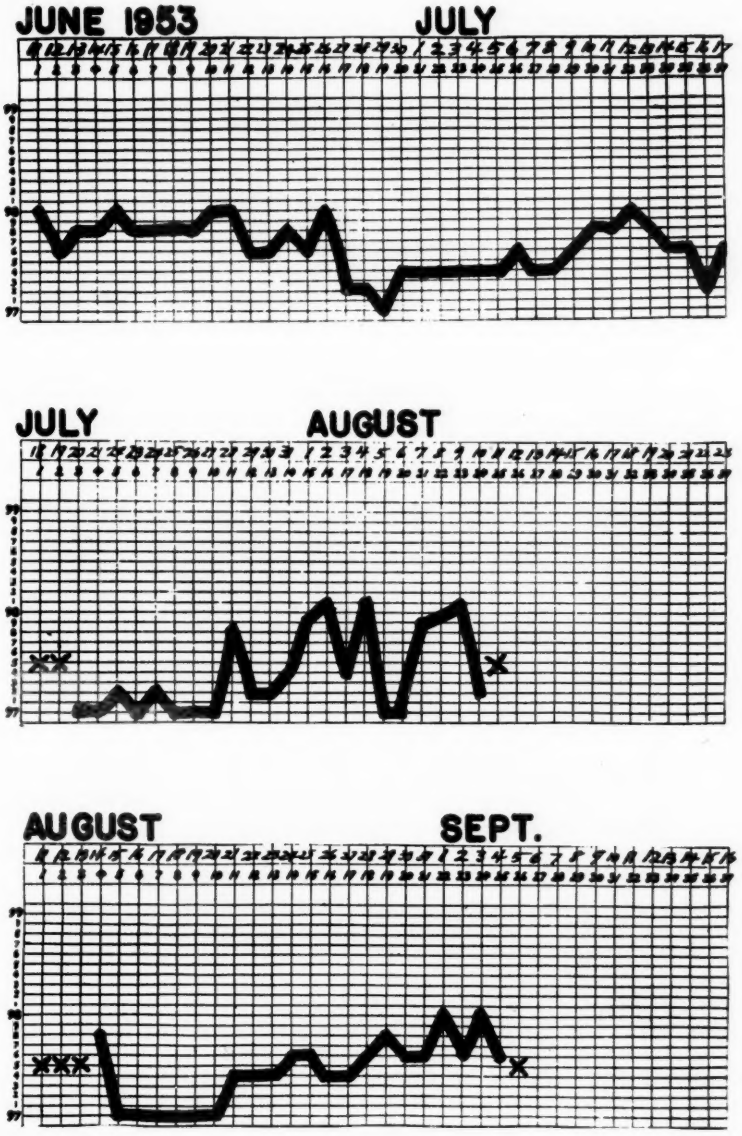


Fig. 1.—Basal temperature chart of Group II patient (aged 30, in whom before treatment the 17-ketosteroids were 30 mg. in 24 hours and who was started on cortisone May 3, 1953.

enlarged clitoris, malformations of the external genitals, skin pigmentation, and short stature, due to early epiphyseal closure. The characteristic laboratory finding of elevated urinary 17-ketosteroids is necessary to the diagnosis. Elevated urinary pregnanetriol is also found and may indeed be the specific metabolite characteristic of the disease.[6] The syndrome is sometimes associ-

ated with abnormal electrolyte metabolism, hypertension, and other disturbances. If untreated, menstruation never occurs, and maturation of the secondary sex organs is absent.

When properly treated with cortisone[7] virilization is arrested, menstruation with ovulation takes place, and the secondary sex organs mature.

The gynecologist's special interest in this group of patients centers about the pathologic changes in the adrenals and genitals as a background to understanding the allied, although less severe, disease encountered as a problem in fertility, and in understanding the anomalies of the genitals he is called upon to correct.

II. Postnatal Virilization Due to Adrenal Hyperplasia.—

This is a relatively less common clinical group of patients in whom there are severe symptoms, including virilization with hirsutism, enlargement of the clitoris, failure of menstruation, failure of development of secondary sex organs, and elevation of urinary 17-ketosteroids. These individuals differ from those of Group I only in that the manifestations are first noticeable after birth, often at the expected time of puberty, and the anomalies of the urogenital sinus derivatives are less severe. These patients require less gynecological surgery. In many discussions in the literature Groups I and II are considered together. The response of these individuals to cortisone therapy is no less dramatic and the accompanying temperature charts illustrate the onset of ovulatory menses in a 30-year-old patient who had never bled prior to cortisone therapy (Fig. 1).

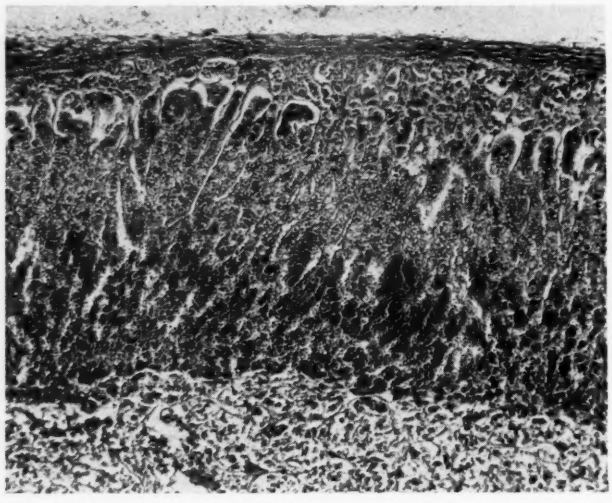


Fig. 2, *A.—For legend see opposite page.*

III. Postpubertal Hirsutism, Oligomenorrhea, and Infertility With Elevated Urinary 17-Ketosteroids, Possibly Due to Adrenal Hyperplasia or an Allied Disorder.—

This clinical group of patients is essentially that described by Jones, Howard, and Langford.[2] These women experience a menarche at the expected time or it may be somewhat delayed. The secondary sex characteristics usually develop normally. Hirsutism may be noted after puberty and is usually mild but there is obvious hair on the chin, upper lip, and cheeks. There is usually more than normal breast hair and the pubic hair is distributed in a triangular fashion. The labial hair is heavy. There are no important ab-

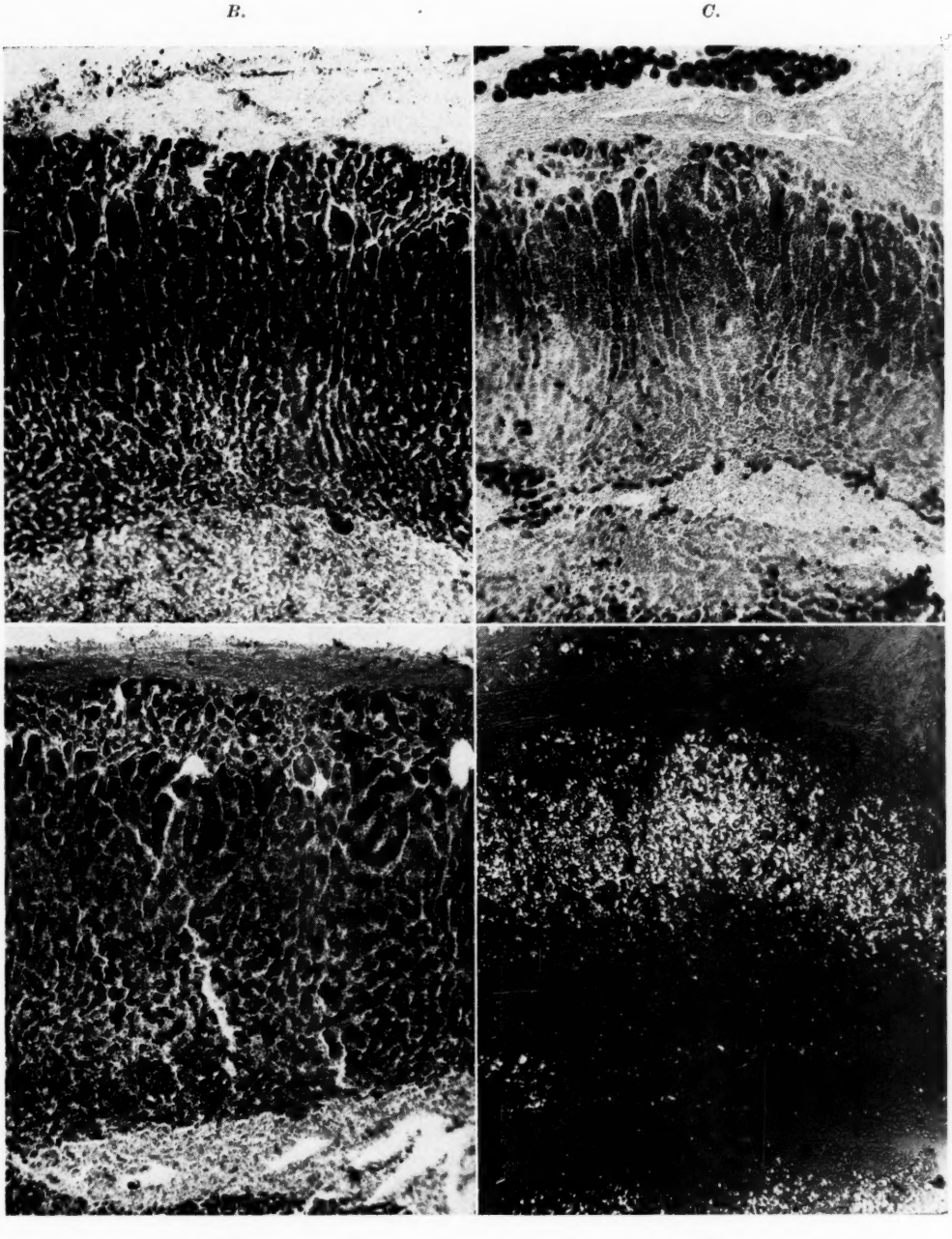


Fig. 2.—Normal adrenal. Woman aged 21. Autopsy specimen. Sudden death.

A, Upper few cells are normal zona glomerulosa. Middle zona fasciculata shows characteristic foamy cytoplasm. The inner one-third of cortex is occupied by zona reticularis characterized by darker staining eosinophilic cytoplasm. A small portion of medulla is also visible. (Hematoxylin and eosin. ×75; reduced ⅓.)

B, Frozen section. Positive for lipid in all layers but especially heavy in fasciculata. Medulla negative. (Sudan black B. ×60; reduced ⅓.)

C, Frozen section. Positive for lipid in glomerulosa and fasciculata and very slightly so in reticularis. Medulla negative. (Sudan III. ×60; reduced ⅓.)

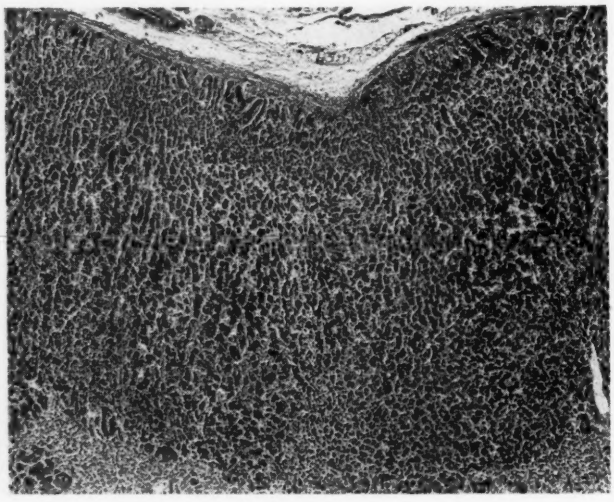
D, Frozen section. All cortical layers positive. Medulla negative. (Ashbel-Seligman technique. ×60; reduced ⅓.)

E, Frozen section. Photographed through crossed polaroid to reveal birefringent crystals which are principally located in fasciculata. Crystals are acetone solvable. (×60; reduced ⅓.)

normalities of the urogenital sinus derivatives, except that the clitoris may be enlarged. The menstrual interval tends to be prolonged and menstruation is either anovulatory or associated with poor luteal function. Infertility is often the presenting symptom and the urinary 17-ketosteroids are mildly elevated. The syndrome can be distinguished from that of Stein-Leventhal by the elevation of the 17-ketosteroids and the normal size of the ovaries. Unfortunately, there has been no opportunity for a pathological examination of the adrenals, but it seems reasonable to view this syndrome as a mild manifestation of classical adrenal hyperplasia or an allied disorder because of the clinical similarity, the elevated urinary 17-ketosteroids, and the response to cortisone.

IV. Postpubertal Hirsutism, Oligomenorrhea, and Infertility With Normal Urinary 17-Ketosteroids but Possibly Due to Adrenal Hyperplasia or an Allied Disorder.—

This clinical group differs in no way from that described in Group III except that the urinary 17-ketosteroids are not elevated. The designation of adrenal hyperplasia as the basis for this group is therefore even more debatable than with Group III. The onset of ovulatory menstruation, however, or the improvement of luteal function following cortisone, and the clinical similarity to Group III cases have led us to think that there must be a very closely related underlying disorder.



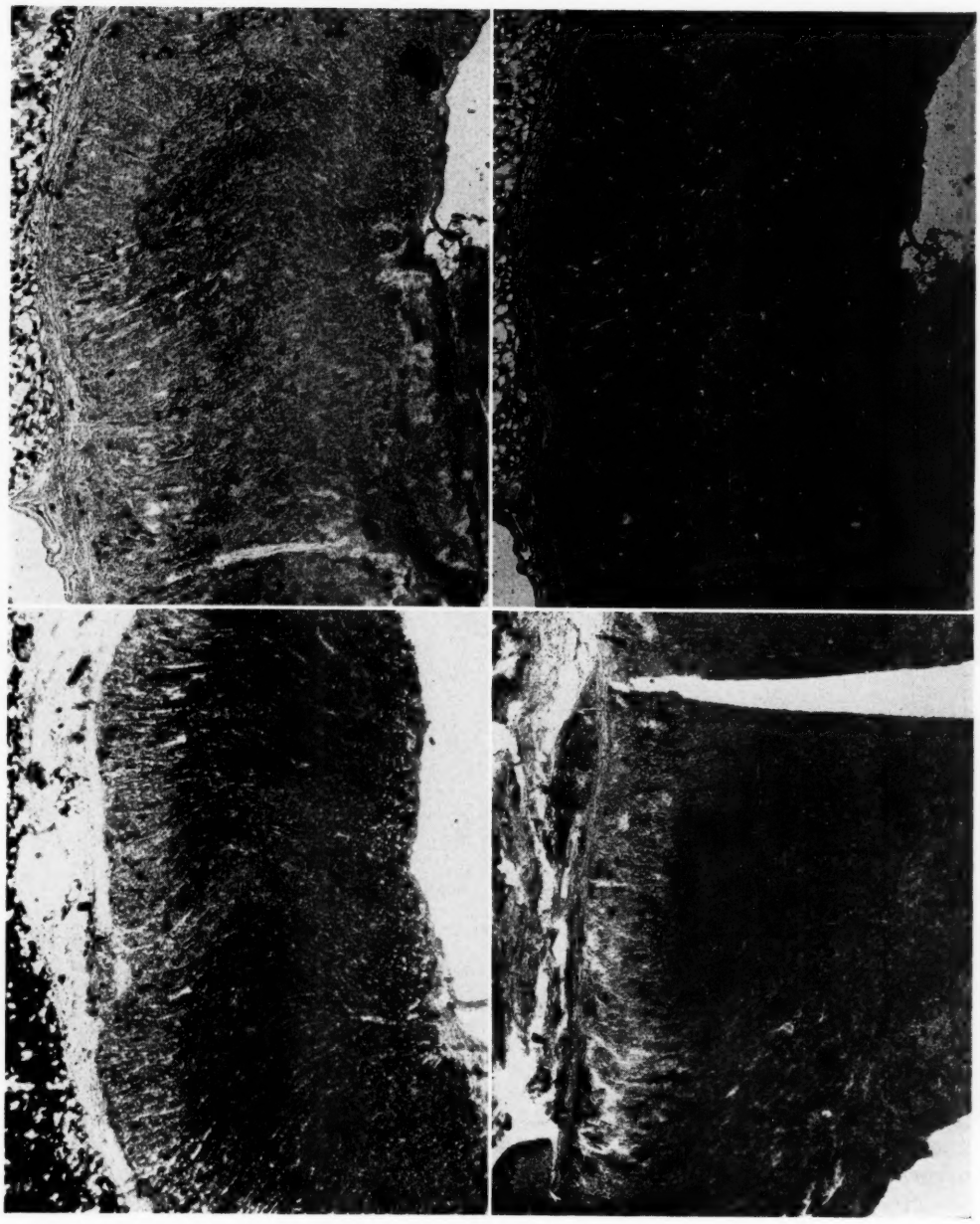
A.

Fig. 3.—Female pseudohermaphrodite. Clinical Group I, aged 29. Autopsy specimen. Death unrelated to adrenal hyperplasia.

A, Tremendous hyperplasia of reticularis. (Hematoxylin and eosin. ×40; reduced ⅓.)
B, Frozen section. Lipid confined to reticularis. (Sudan black B. ×40; reduced ⅓.)
C, Frozen section. The glomerulosa-fasciculata negative. Reticularis positive. (Sudan III. ×40; reduced ⅓.)
D, Frozen section. Principle activity in reticularis. (Ashbel-Seligman technique. ×40; reduced ⅓.)
E, Frozen section. Crossed polaroid. Birefringent crystals confined to reticularis. (×40; reduced ⅓.)

Adrenal Pathology

Blackman[8] described the adrenal changes in 4 cases of female pseudohermaphroditism in his careful study of the function of the reticular zone of the adrenal cortex. He concluded that hyperplasia of the reticular zone was a constant observation in such cases; however, he further pointed out and described similar reticular hyperplasia with Cushing's syndrome and other un-



C. E. B. D.

Fig. 3, *B, C, D, E.—For legend see opposite page.*

classified cases exhibiting hirsutism. His general conclusion was that this layer was associated with the metabolism of the masculinizing sex hormone. The sparsity of pathological reports in the literature, together with the development of histochemical methods which purport to demonstrate the presence of ketosteroids in tissue, makes pertinent a review of the pathological adrenal changes.

There were available for study from clinical Group I, 7 autopsy specimens, including the 4 previously reported by Blackman, and 6 surgical specimens, 3 of which are included (but only briefly described) in Young's monumental work.[4] There were also available 2 surgical specimens from clinical Group II. Slides of paraffin blocks were available on all 15 cases, and, in addition, it was possible to locate formalin-fixed material from 6 autopsy cases, and one surgical case. The formalin material was used to attempt lipid and ketosteroid localization. There were then available for study on all cases paraffin sections stained with hematoxylin and eosin. In addition, in some cases, paraffin sections were also stained with Masson's trichrome method, iron hematoxylin, and Wilder's reticulum stain. Frozen sections were stained with sudan III, sudan black B, and by the Ashbel-Seligman method[9] for ketosteroids. Sections were also examined for birefringence and acetone solubility.

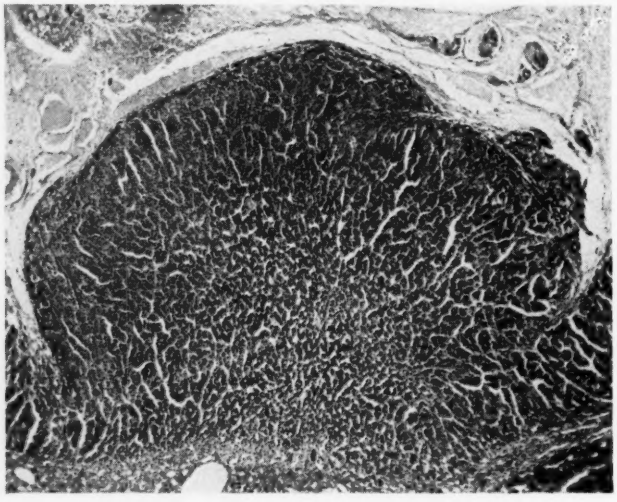


Fig. 4, *A.—For legend see opposite page.*

Deane and Greep[10] and others[9, 11, 12, 13] have maintained that ketosteroids react positively to such lipid procedures as mentioned, even though no one test is specific. They consider a positive reaction to the entire group, however, as presumptive evidence of the presence of ketosteroids. Other investigators[14, 15, 16, 17] have held that such methods were not specific enough for exact ketosteroid localization. Fortunately for the purpose at hand, the controversy need not be of critical concern as will be indicated.

The autopsy material consists of 7 patients, aged 7 and 13 days, 3 and 6 weeks, 3, 29, and 31 years. The surgical material consists of 8 patients, aged 5 months, 6 years (2 cases), 7, 13, 16, 19, and 20 years. All patients were typical female pseudohermaphrodites with enlarged clitoris and a single external opening of a urogenital sinus into which the vagina entered except for the 2 clinical Group II patients, aged 19 and 20, who had separate vaginal and urethral openings. Two had been reared and named as males. None had

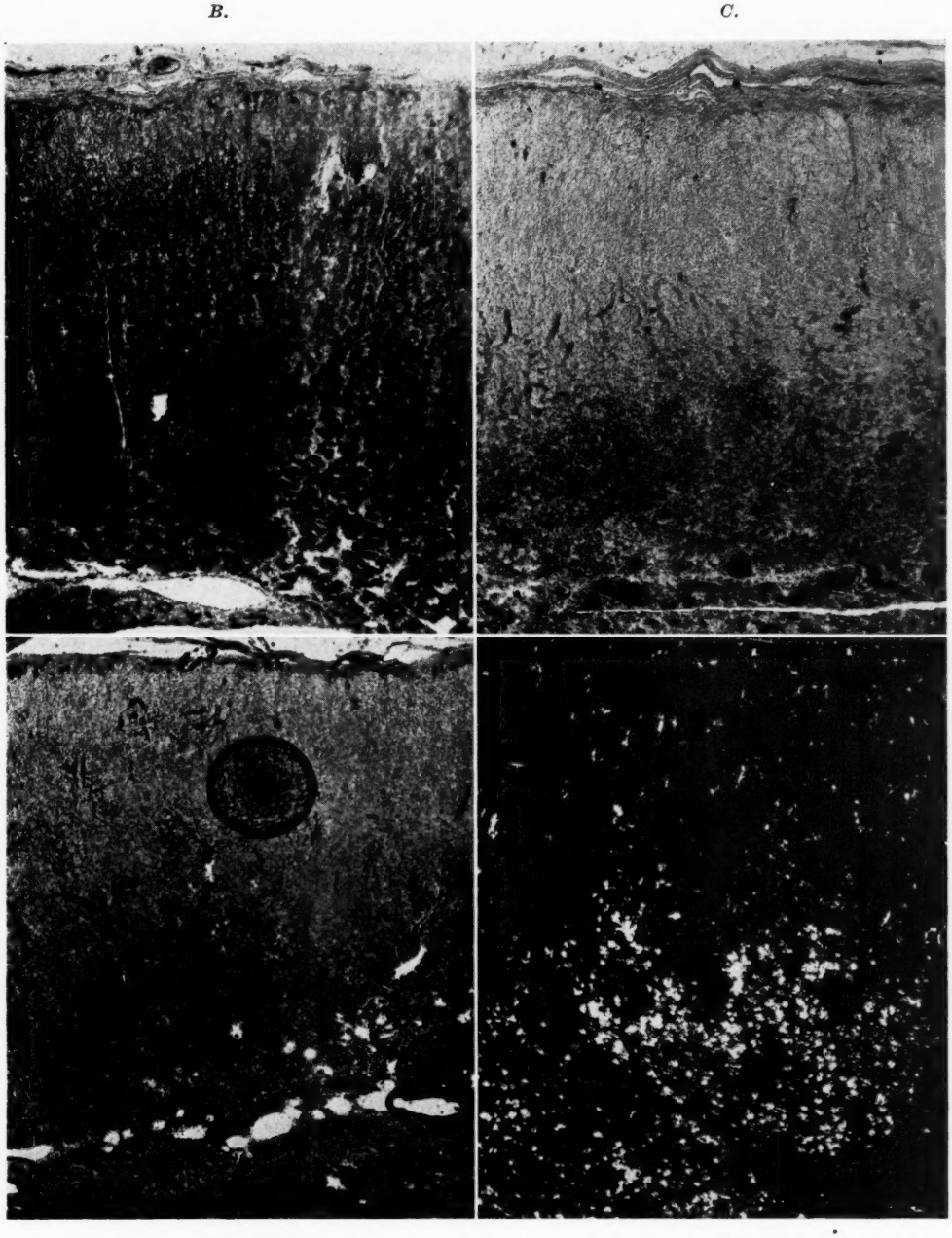


Fig. 4.—Female pseudohermaphrodite. Clinical Group I, aged 5 months. Surgical specimen. Severe electrolyte disturbances.

A, There is a tremendous hyperplasia of reticularis, which at this age would be expected to occupy a layer but a few cells wide. The glomerulosa is sparse but the fasciculata is present. It does not, however, exhibit the usual vacuolated cytoplasm. (Hematoxylin and eosin. ×50; reduced ⅓.)

B, Frozen section. Lipid confined to reticularis. (Sudan black B. ×60; reduced ⅓.)

C, Frozen section. Lipid confined to inner reticularis. (Sudan III. ×50; reduced ⅓.)

D, Frozen section. Activity only in inner reticularis. (Ashbel-Seligman technique. ×40; reduced ⅓.)

E, Frozen section. Crossed polaroid. Birefringent crystals confined to reticularis. Acetone soluble. (×50; reduced ⅓.)

menstruated. All were hirsute and of typical stature. The 4 youngest autopsied children died of the disease, presumably as a result of disturbance of electrolyte metabolism, and one died after an intercurrent acute illness of eighteen hours, while under cortisone therapy. The other deaths were not caused by the disorder. Exploratory operations were done in the surgical cases in an attempt to alleviate the condition. This procedure is of course no longer practiced.

The adrenals in all cases were greatly enlarged over the normal size for the age. The largest adrenal glands weighed 80 and 90 grams, respectively, compared to a normal adult weight of about 10. The infant glands were three to five times the expected weight for the age. Grossly, the outer layers of the normal cortex are yellow and the inner, or reticular layer, is thin and light brown. In adrenal hyperplasias, the pathologist at the time of autopsy uniformly described the fresh adrenals as being composed of an outer pale or white zone in addition to a darker brown or reddish inner zone. In 3 of 6 instances he commented that the cortex apparently was depleted of fat.

Microscopically all cases showed some degree of hyperplasia of the reticular zone of the cortex. In general the degree of hyperplasia seemed to increase with age. It is most easily seen in adults where upward of 90 per cent of the cortex may be occupied by reticularis compared to a normal adult composition of from one-fourth to one-third of the cortical width (Figs. 2, *A*, 3, *A*).

An estimation of the degree of reticular hyperplasia in infancy and childhood depends upon a comparison of the gland in question with the expected reticular width for the age. According to Blackman,[8] and in agreement with other studies, the fetal reticular zone normally disappears by the end of the first month of postnatal life. The adult reticular zone, lying next to the fascicular zone and composed of cells smaller and with darker nuclei than those of the fetal reticular zone (hematoxylin and eosin) first appears as a thin layer at about 1 week of age. This layer gradually enlarges and becomes pigmented until it occupies its adult proportion of one-fourth to one-third of the cortical width at about puberty. In infant pseudohermaphrodites there is great hyperplasia of the adult reticular zone, and in all instances this zone occupied well over half the cortex, even in the patient who died at the age of 7 days. The hyperplasia of adult reticularis is therefore very great when compared with the expected reticular development at the corresponding age (Fig. 4, *A*).

The fetal reticularis does not participate in the hyperplasic process. Fetal reticularis was present in the 5 patients under 5 months of age, but was less noticeable with increasing age until in the case of 5 months it was scarcely present. In the very young glands (7, 13, and 21 days), it was not easy to be sure of the demarcation between fetal and adult reticularis, but careful study, especially with the lipid preparations, resulted in a satisfactory diagnostic separation.

In addition to reticular hyperplasia, the glands under discussion exhibited other abnormalities. In the 4 infants who died and in the gland removed surgically at 5 months, the glomerular layer, which is said to be concerned with electrolyte metabolism[13] was practically absent although in 2 cases a few cells, apparently belonging to the glomerulosa, could be seen within the fibrous capsule. In other cases the glomerulosa seemed normally formed or actually hyperplastic. In the adult of 29, the glomerular area was about 30 layers deep compared to a normal of about 5. In 8 instances there was considered to be some degree of glomerular hyperplasia (Fig. 5). It may be significant that the 4 infants with deficient glomerulosa seemed to die in Addisonian crisis.

The fascicular zone also exhibited marked variation. There was recognizable fasciculata in all cases. In the adults, aged 29 and 31, it was no more

than 10 cells thick compared to a normal of 30 to 50, and in some areas was absent. This variation in fasciculata in various areas of the same gland was characteristic of most of the glands. The fasciculata normally contains spongy vacuolated cytoplasma (hematoxylin and eosin), but in the cases under dis-

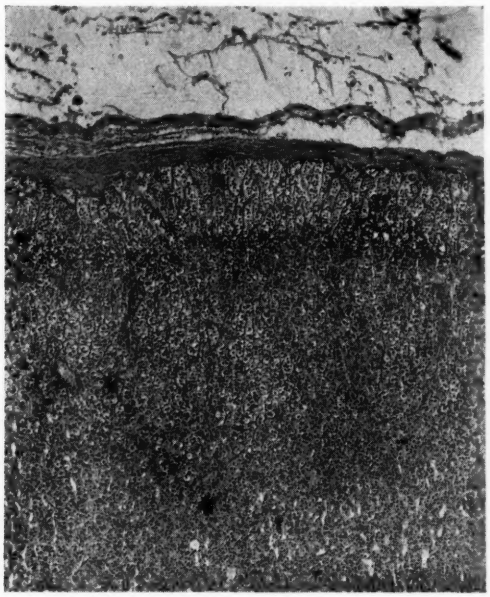


Fig. 5*A*.—Female pseudohermaphrodite, aged 20. Low power. Same patient as illustrated in Fig. 1. Adrenal biopsy. Glomerulosa 30 cells deep compared to a normal of about 5. This gland has a much more normal fasciculata than any gland from clinical Group I patients. The reticularis is very hyperplastic as shown in Fig. 5*B*.

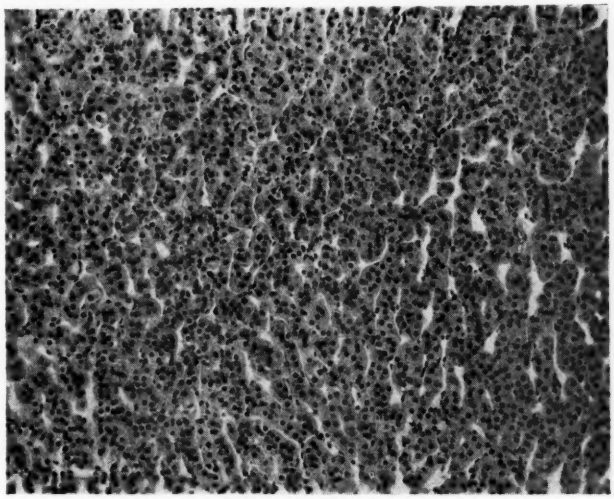


Fig. 5*B*.—High power of hyperplastic reticularis.

cussion the fasciculata for the most part exhibited homogenous eosinophilic cytoplasm. The fasciculata seemed to become less prominent with increasing age. In some areas in one case of Group I the fasciculata exhibited some vac-

uolated cytoplasm. In the two glands from clinical Group II the fasciculata was more normal and contained cells with more prominent vacuolization (Fig. 6).

Formalin material was available for frozen sections from 6 autopsied and one surgical patient. One autopsied patient was treated with cortisone. The studies showed no lipid with any of the techniques used in glomerulosa or fasciculata, except in the cortisone-treated patient. The hyperplastic reticularis, however, exhibited substantial lipid with sudan black B in 5 of the 7 specimens. The fetal reticularis, when present, also reacted positively. There were decreasing amounts of reticular lipid to sudan III, Ashbel-Seligman ketosteroid method, and birefringence. The lipid was acetone soluble (Figs. 2, *B* to *E*, 3, *B* to *E*, and 4, *B* to *E*).

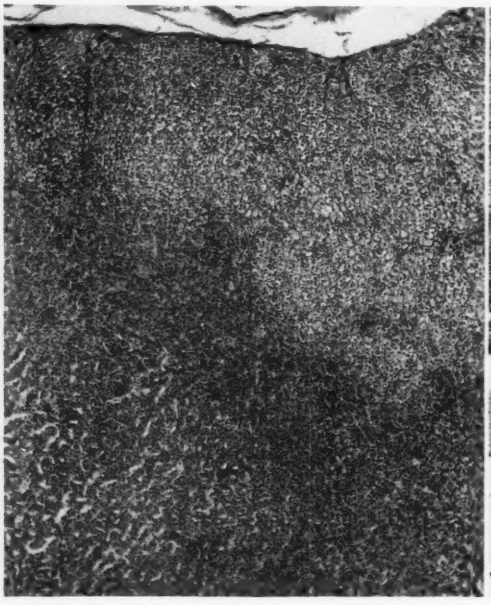


Fig. 6.

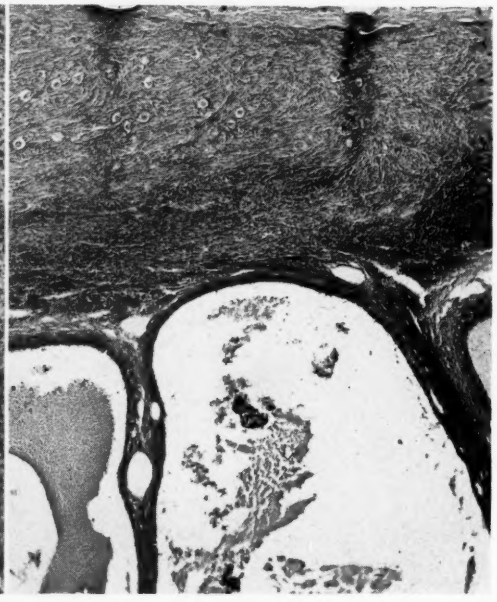


Fig. 7.

Fig. 6.—Female pseudohermaphrodite, aged 19. Lower power. Adrenal biopsy. The fasciculata is especially prominent in this area and approaches normal in thickness and cellular vacuolization. The reticularis is quite hyperplastic.

Fig. 7.—Ovarian biopsy from same patient illustrated in Fig. 6. Low power. The cortex contains numerous primordial follicles. Other follicles have developed almost to the point of small cysts.

The absence of lipid from the fasciculata, together with its anatomical deformity, may be of considerable importance in view of the probability that this layer is concerned with production of the glucocorticoids.[13]

It is important to note that the significance of the absent fascicular and glomerular lipid is somewhat obscured by the fact that, in autopsy material, adrenal lipid depletion is not uncommon in a variety of illnesses. We are led to believe, however, that the finding as recorded is probably significant, as a study of 25 adrenals by the above methods showed lipid in the reticularis in very few instances and only when there was considerable fascicular lipid. This finding is in confirmation of the more extensive and exhaustive study of Ayres, Ferminger, and Hamilton[18] on adrenal lipid depletion in various disease states. In addition, Benua and Howard[19] have studied the in-

fant cortex in autopsy material by means of the Ashbel-Seligman technique and have reported staining throughout, although in some instances the reticularis appeared most intense.

Furthermore, in the one surgical specimen available for lipid staining, the finding is similar and very clear (Fig. 4). The examination of adrenals removed surgically for various conditions shows only minor fascicular lipid depletion as judged by vacuolated cytoplasm of hematoxylin and eosin stained paraffin material. The findings in the surgically removed gland seems to make the autopsy observations more valid. Nevertheless, it is obvious that the limited series of cases and the difficulties with adrenal lipid depletion in various conditions make the conclusion in regard to adrenal lipid distribution somewhat less than binding. The observation tallies so well, however, with the known endocrine aspects of the disease that it would not be unreasonable to suppose that it indeed accurately reflects the status in vivo.

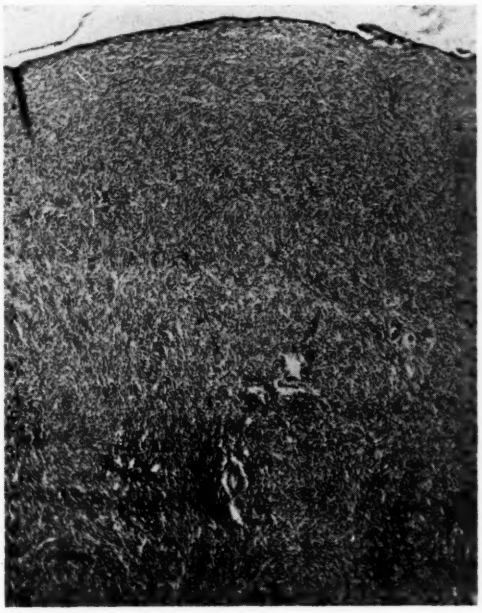


Fig. 8.—Ovarian biopsy from same patient illustrated in Fig. 2. Cortex has no discoverable follicular elements. (×50; reduced ⅓.)

As mentioned previously, the localization of ketosteroids by a battery of lipid tests is at best debatable. It is interesting, however, that some cells of the reticularis seemed to be positive to all lipid tests applied. As this is the only stainable "ketosteroid" in these cases, this may be confirmation of the conclusion reached by Blackman on circumstantial evidence that the reticularis was the site of the masculinizing stimulus in such patients.

The only exception to the lipid distribution previously described occurred in the gland of the child who died within eighteen hours of poisoning or a fulminating infection after being under therapy for about three years with cortisone. In this case there was recognizable reticular hyperplasia but much less than in untreated cases. Furthermore, lipid was present in all cortical layers with sudan black B and sudan III, but only in the reticularis with the Ashbel-Seligman technique.

The adrenal changes may be summarized by noting that the great adrenal enlargement seems to be due principally to reticular hyperplasia, and that this hyperplasia apparently becomes more marked with increasing age. In some instances the glomerulosa may also participate in the hyperplasia although in the 4 cases of fatal electrolyte depletion the glomerulosa was atrophic. The fasciculata is sometimes partially absent and seems to become less prominent with advancing age. In all cases studied that were not treated by cortisone there was depletion of fascicular and glomerular lipid while there was a positive lipid reaction and a positive test presumptively for ketosteroid in the reticularis in 5 of 7 cases tested.

Ovarian Pathology

Ovarian tissue or sections were available from all 15 cases where the adrenals were studied and in 2 additional cases from Clinical Group I. In the infants the ovaries showed no change from normal. There were abundant primordial follicles, some of which had developed to become macroscopically visible, but none greater than 4 mm. in diameter. A few antrum follicles were seen. Atretic follicles were also noted. The ovarian stroma was normally sparse. The ovary in older untreated pseudohermaphrodites becomes increasingly abnormal. In the teen-aged individuals there were also primordial, developing, and atretic follicles, but no sign of recent or previous ovulation (Fig. 7).

The ovaries of the 29- and 32-year-old women were greatly abnormal for their age. There were no primordial follicles and no developing or atretic follicles. The ovarian cortex consisted of ovarian stroma. In one of these ovaries there were a few hyaline structures suggesting very old corpora albicantia although there was no history of menstrual bleeding (Fig. 8).

There was also no sign of luteinization about the developing or atretic follicles in clinical Group I cases. In the 2 cases from clinical Group II there was some luteinization (Fig. 9). Primordial follicles could also be found. It may be significant that the case with the best luteinization had the most normal fasciculata (Fig. 6).

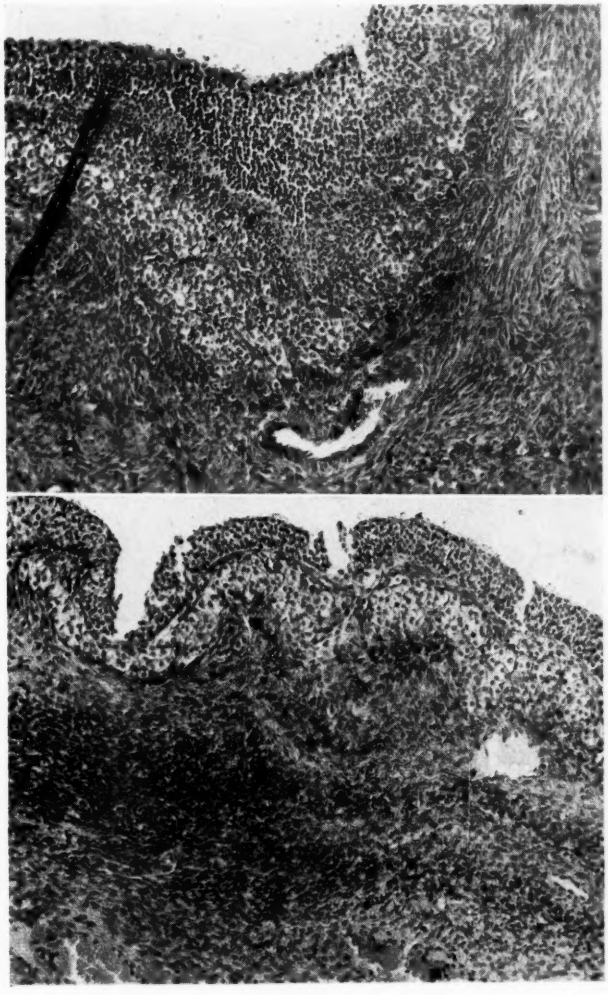
The ovarian changes in Group I and II cases of adrenal hyperplasia may be summarized by pointing out that in infants, children, and teen-agers there seems to be normal follicular development to the antrum stage but no evidence of ovulation. As patients become older there is less and less follicular activity and a disappearance of primordial follicles. It should be noted, however, that this disappearance must not be as complete as it seems to be microscopically, because cortisone therapy, even in adults, finally results in ovulatory menstruation after a treatment period of four to six months.

Developmental Anomalies of the Genital Tubercle and Urogenital-Sinus Derivatives

The study of a relatively large number of cases of pseudohermaphroditism due to congenital adrenal hyperplasia has indicated that the Wolffian ducts atrophy in the usual manner.[20] Furthermore, the Müllerian derivatives are uniformly present but in an undeveloped state. There are, however, serious anomalies of the urogenital-sinus derivatives, including that part which unites with the genital tubercle to form the clitoris. For the most part these anomalies have been described by urologists, who are accustomed to thinking of the urethra as extending from the bladder to the end of the phallus. The vagina is therefore described as entering the urethra. The gynecologist, on the other hand, considers the urethra as extending from the bladder some 4 cm. to the vaginal vestibule. The circular muscle fibers along its entire length

have an important sphincter action. Therefore, to think of the vagina entering this structure implies an important problem of urinary continence in the surgical correction of the anomaly. The descriptions in the literature of the point of entrance of the vagina in relation to the urethral sphincter mechanism are by no means clear. In view of the fact that the lower part of both the vagina and the female urethra arise from the urogenital sinus, there are reasons in embryology to be concerned about this point.

A.



B.

Fig. 9.—*A*, Ovarian biopsy from same patient illustrated in Figs. 1 and 5. There is some luteinization of theca. (×150; reduced ⅓.)
***B*, Ovarian biopsy from same patient illustrated in Fig. 6. Luteinization of theca. Luteinization observed only in the two clinical Group II cases. It is these cases which exhibited the more normal-appearing fasciculata. (×150; reduced ⅓.)**

Normally, according to Greene,[21] the cranial portion of the urogenital sinus in the female gives rise to a portion of the bladder, the urethra, the paraurethral (Skene's) glands, and Bartholin's glands. In the male, part of the bladder, the prostatic urethra, the prostate, and Cowper's glands are derived from the cranial urogenital sinus. The caudal portion of the sinus

in the female gives rise to the vaginal vestibule, the inner surface of the labia minora, and the minor vestibule glands. In the male it yields the membranous urethra, the cavernous urethra, and the periurethral glands.

The genital tubercle yields the clitoris and prepuce in the female and the homologous structures in the male. In order to clarify the surgical anatomical considerations and to show the transition in the various clinical groups under discussion, the diverse anomalies have been catalogued with special reference to the relation of the vagina to the urethra.

For this purpose there are available in the records of the Johns Hopkins Hospital 33 cases of congenital adrenal hyperplasias (Group I); 7 cases of postnatal virilization (Group II), 16 cases of postpubertal hirsutism with elevated 17-ketosteroids (Group III), and 15 cases of postpubertal hirsutism with normal 17-ketosteroids (Group IV).

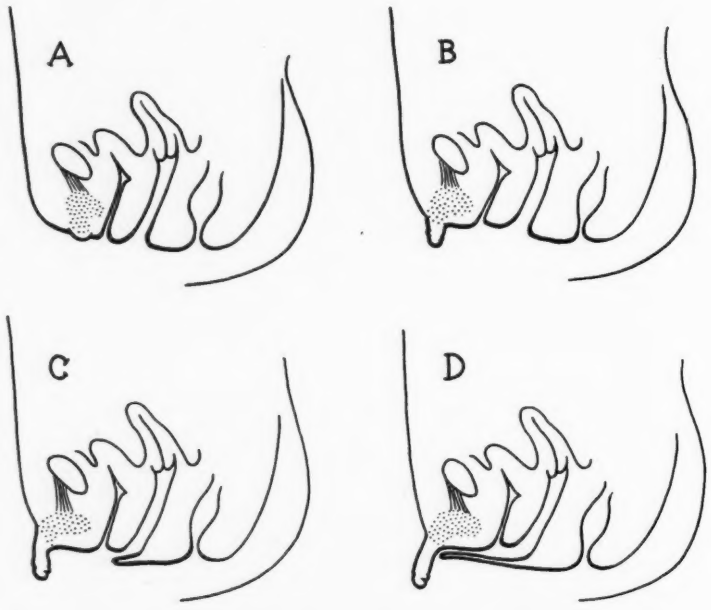
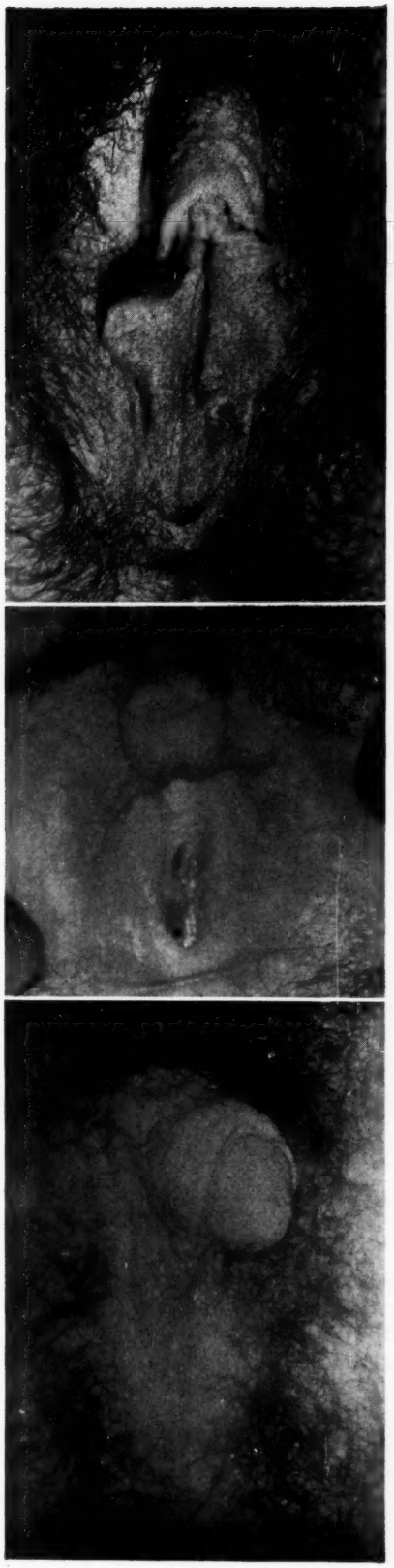


Fig. 10.—Diagrams to show degrees of abnormalities of urogenital-sinus derivatives. The groups are explained in detail in the text.

The findings in regard to the urogenital-sinus derivatives and phallus have been classified into four anatomical groups (Fig. 10). Group A has normal female urogenital-sinus derivatives and a normal-sized phallus. Group B has essentially normal female sinus derivatives but an abnormally large clitoris. The clitoris in most cases of Group B is only slightly enlarged but in a few has been quite sizable (Fig. 11, *A*).

In Group C the sinus develops slightly in the direction of the male (Fig. 11, *B*). The vagina and urethra open into the vestibule although it may be necessary to retract the remnants of the sinus posteriorly in order to see the vaginal opening. The opening is often funnellike and in an infant may be relatively large, measuring 1.5 or 2 cm. in diameter. The clitoris is enlarged. In Group D the sinus has developed markedly toward the male structures (Fig. 11, *C*). Neither the female urethral meatus nor the vagina is visible

Fig. 11.—*A*, External genitals. Anatomical Group B. Patient from clinical Group III.
B, External genitals. Anatomical Group C. Patient from clinical Group II.
C, External genitals. Anatomical Group D. Patient from clinical Group I.



A.

B.

C.

Fig. 11.—*For legend see opposite page.*

but the external meatus of the urogenital sinus is located more or less at the base of the enlarged phallus. Endoscopy or roentgen examination after the injection of a radiopaque substance is necessary to establish the relation of vagina and urethra and to determine the competence of the urethral sphincter. The labia minora are absent and there is a median raphe in the perineum as in the male. The labia majora (which are not derived from the sinus but from the so-called labioscrotal folds) are present and may suggest a cleft scrotum as they are sometimes fused posteriorly. As the clitoris is greatly enlarged, the external meatus of the sinus at the base of the phallus suggests a condition of male hypospadius.

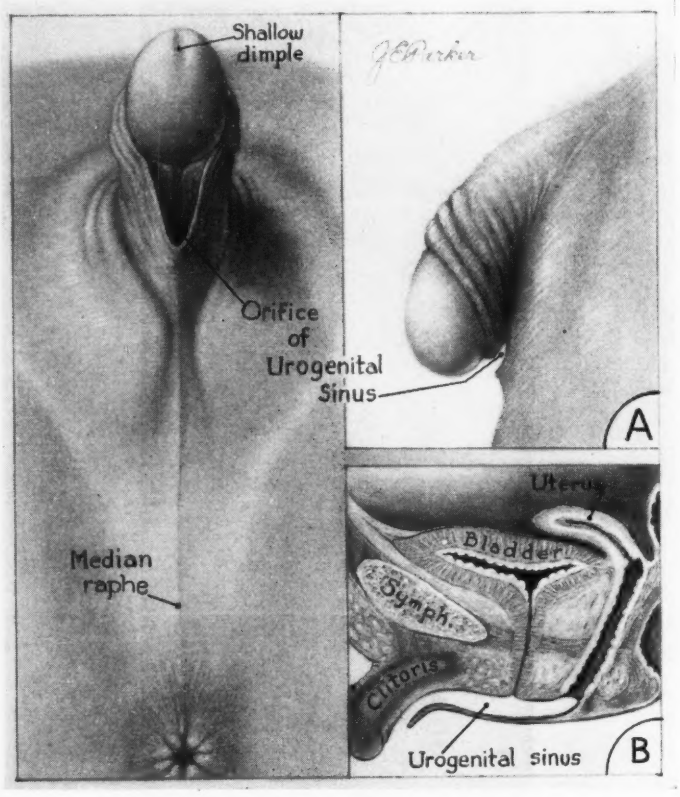


Fig. 12A.—Preoperative situation of patient classified as clinical Group I, anatomical Group D.

It is important to note that these anatomical groupings are arbitrary in the extreme, and in reality they blend one into the other, especially Groups C and D, where the tendency toward male sinus derivatives is largely of degree.

TABLE I. ANATOMICAL ABNORMALITIES ACCORDING TO CLINICAL GROUPS

CLINICAL GRUOPS	NO. CASES	ANATOMICAL ABNORMALITIES			
		A	B	C	D
I	33	0	0	7	26
II	7	0	3	4	0
III	16	9	7	0	0
IV	15	8	7	0	0

Table I shows the distribution of clinical groups in relation to the anatomical groupings. The results in this table indicate that the masculinization of the urogenital sinus derivatives parallels the severity of the clinical symptoms. Wilkins[20] has pointed out that in the normal embryo the Wolffian duct has disappeared before the 63 mm. stage and the vaginal and urethral orifices have become separated by the 162 mm. stage. It therefore seems reasonable to suppose that the masculinization effect has become manifest between these two stages.

In clinical Group I, where extensive surgical reconstruction of the genitals is necessary, the findings may be noted in greater detail. Three of these individuals were reared as males. Six of the 33 patients had a degree of chordee sufficient to be commented upon by the original examiner. Fourteen

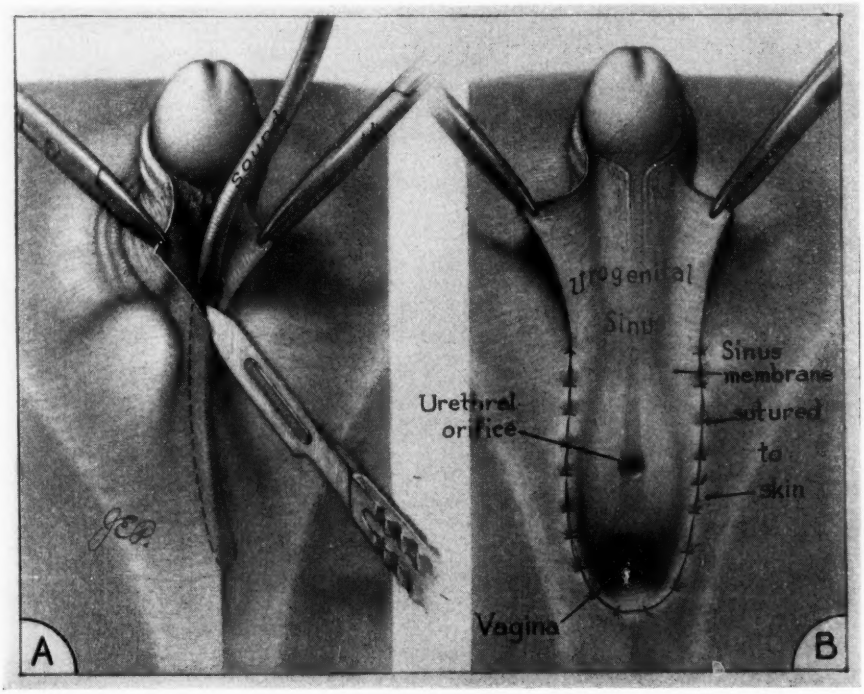


Fig. 12*B*.—*A*, The urogenital sinus is incised on an instrument. The opening of the sinus reveals the female urinary meatus to be in its normal position.
B, The sinus membrane is sutured to the skin after trimming away any excess. In this case the edges related to the vagina could be brought to the skin with little or no tension. In some instances it is necessary to free the vagina posteriorly and laterally to place the sutures without tension.

of the 33 were endoscoped so that exact measurements and the relationship of urethra to vagina is known. In one case there seemed to be no communication between the urogenital sinus and the vagina, which was found to be present at laparotomy. All patients had good urinary control. In no case did the vagina communicate with that portion of the urogenital sinus which gives rise to the female urethra in the case of a female or the prostatic urethra in the case of a male. The vaginal communication was always in relation to the caudal urogenital-sinus derivatives so that the sphincter mechanism is fortunately not involved and the anomalous communication is with that portion of the sinus yielding the vaginal vestibule in the female and the membranous urethra in the male. From the point of view of the gynecologist, it is much

clearer to speak of the vagina and (female) urethra as entering a persistent urogenital sinus rather than to speak of the vagina as entering the (membranous male) urethra. These anatomical considerations are of considerable importance in the operative correction of the condition as will be noted later.

The Gynecological Management of Pseudohermaphroditism and Postnatal Virilization Due to Congenital Adrenal Hyperplasia—Clinical Groups I and II

It has been only since the beneficial effects of cortisone have been known that the gynecological surgeon has played an important part in the therapy of individuals with severe adrenal hyperplasia. With the onset of menstruation it has become important to provide a suitable passage for the menstrual

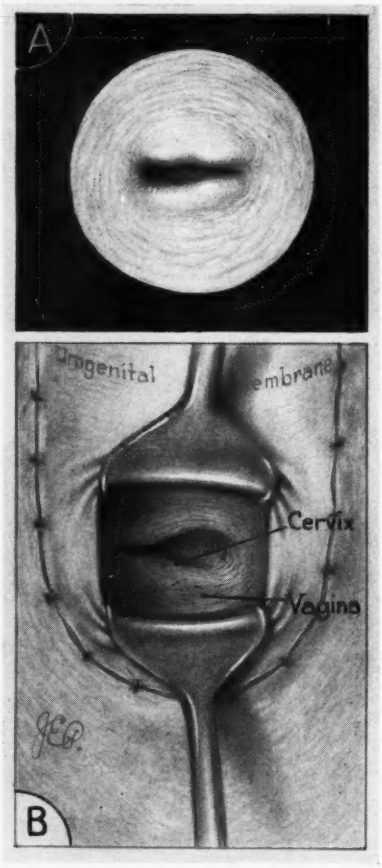


Fig. 12*C*.—*A*, The cervix and vagina are revealed through a McCarthy panendoscope, the vagina distended with water.

B, The operative view of the vagina and cervix which has very little substance.

blood. Furthermore, the induction of ovulatory menstruation implies the possibility of pregnancy and the desirability of a functioning vagina. The gynecologist is therefore called upon to undertake the reconstruction of the external genitals. The general medical management, including the proper dosage of cortisone, has been fully discussed by Wilkins and co-workers[7] and will not be further elaborated here.

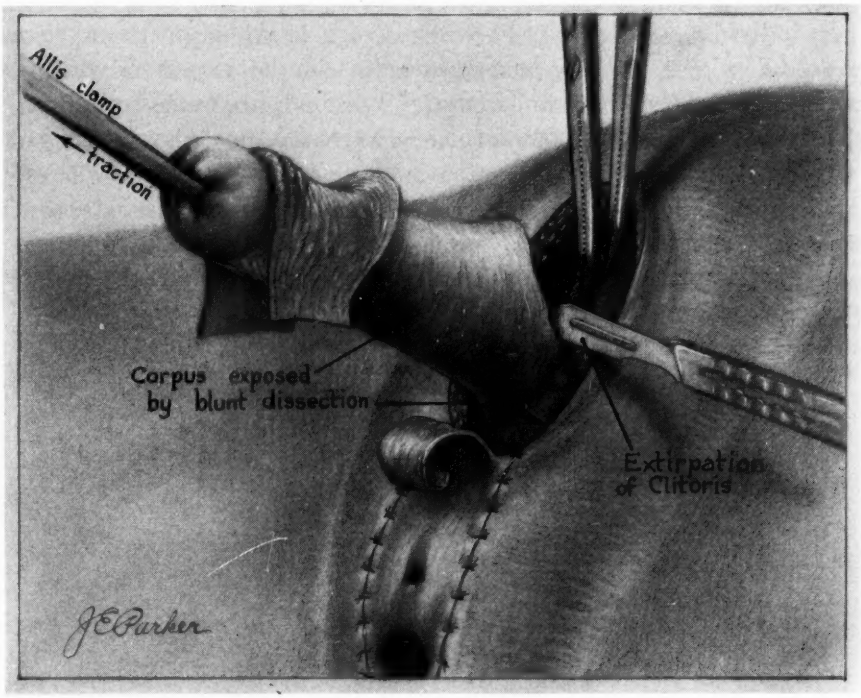


Fig. 12*D*.—The incisions for extirpation of the clitoris. After carrying the incision circularly around the base of the clitoris superiorly and laterally, the incision is fashioned on the ventral surface in such a way that a flap of sinus mucous membrane is preserved for construction of a small nonerectile clitoris.

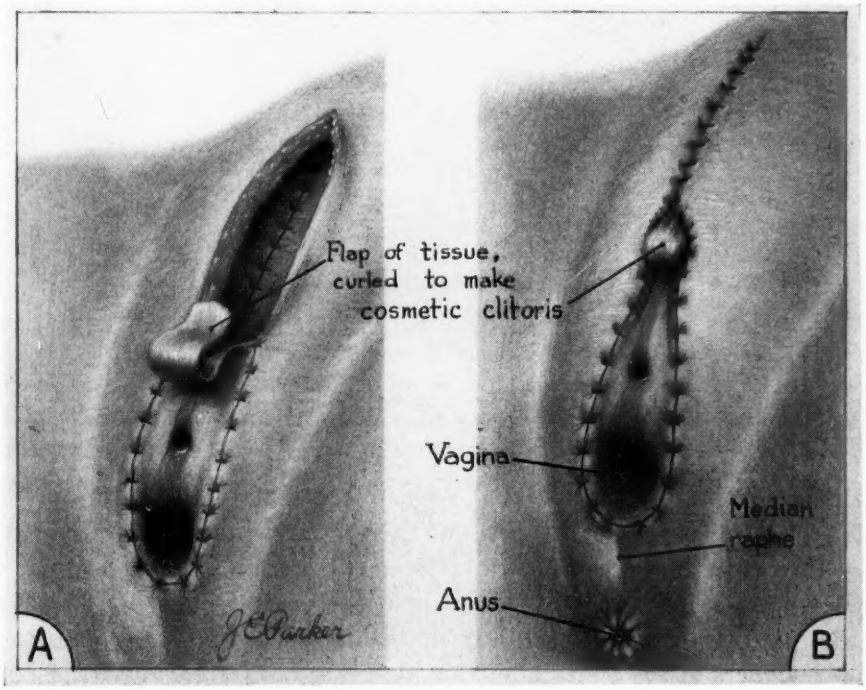


Fig. 12*E*.—The final stage.

The operative procedure may be considered under three circumstances. First, in individuals over 8 to 10 years of age in whom cortisone therapy is planned and whose puberty and menarche can be expected within a few weeks or months after initiating therapy. Second, in younger children, without electrolyte disturbances, not previously treated, but who, because of their age, will not experience puberty or a menarche for several months or years. Third, in individuals with electrolyte disturbances, who are already under cortisone and other therapy.

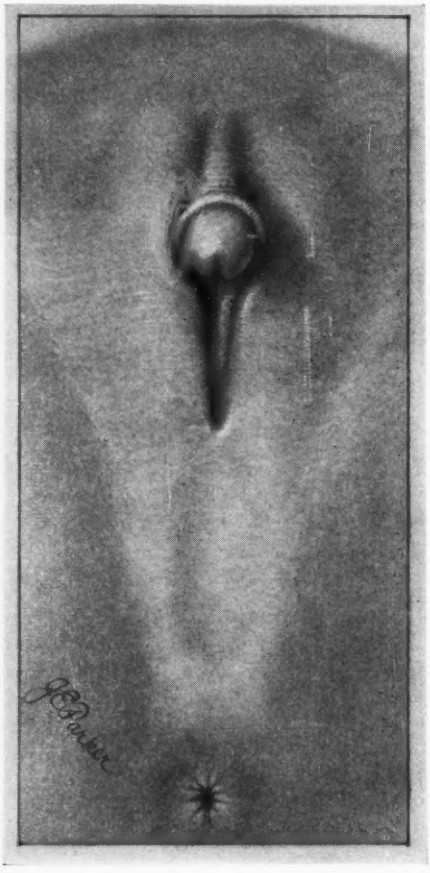


Fig. 13*A*.—The preoperative situation in an 11-year-old, clinical Group I, anatomical Group C, pseudohermaphrodite. The sinus opening is much lower than in Fig. 12*A* and is funnellike and wide. A small retractor or finger inserted into the opening will reveal the vagina and urethra.

Under the first circumstance it seems clear that the operative procedure should be undertaken prior to cortisone therapy, although the cortisone dosage is probably not large enough to interfere with normal wound healing. Furthermore, there seems to be no worry about postoperative adrenal insufficiency as no trouble has developed in any of the 19 individuals operated upon by various members of the staff under this plan.

In children in whom puberty and vaginal estrogenization are not to be expected for months or years, the question arises as to whether early operation might result in contraction of the new vaginal outlet. This occurred in one case. The psychological advantage of operation in early childhood, however, probably justifies the possible risk of contraction. Nevertheless, the time of operation under these circumstances must remain an open question.

To date no infant in this series, who had a serious electrolyte problem, has been operated upon. With supplementary preoperative and postoperative cortisone therapy, however, no serious problem is anticipated. It should perhaps be noted that all patients who receive cortisone regularly, regardless of electrolyte status, have received supplementary pre- and postoperative cortisone.

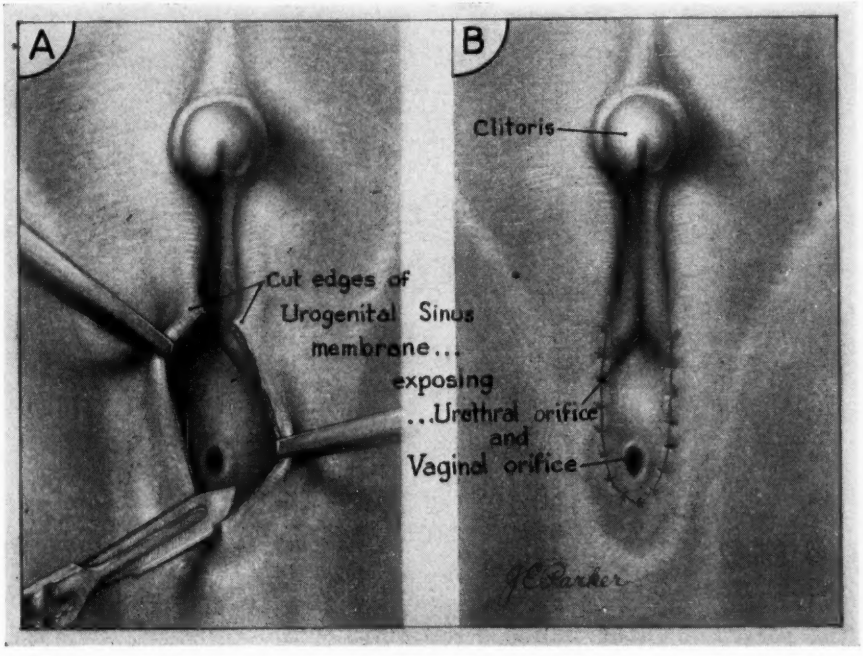


Fig. 13*B*.—*A*, The incised urogenital sinus, the membrane of which forms the new vaginal vestibule.
B, The suturing of the sinus membrane to the skin after excision of the excess tissue.

The essential stages in the operative procedure for plastic reconstruction of the external genitals for defects of anatomical Group D were devised by Hugh Young,[4] who first carried out such a procedure in 1934, although he himself later reported it erroneously as in 1936. The steps of the operative procedure as modified are shown in Fig. 12. Several points may be emphasized. There is some variation in the ease with which the edges of the new vaginal vestibule can be sutured to the skin. The amount of subcutaneous fat has an important bearing on this point, but in only one case did the sutures pull out sufficiently to cause outlet scarring.

TABLE II. CLINICAL DATA OF PATIENTS IN GROUP III

PATIENT	AGE	AGE AT MENARCHE	YEARS OF AMENORRHEA	YEARS OF OLIGOMENORRHEA	DEGREE HIRSUTISM	YEARS OF INFERTILITY	DEGREE CLITORIS ENLARGEMENT	17-KETOSTEROIDS		RESULT	
								BEFORE CORTISONE	AFTER CORTISONE	MENSES	FERTILITY
1	17	15	2	–	++	0	0	15.4	6.0	Ovulatory	–
2	30	17½	–	12½	+	7	+	17.1	6.9	Ovulatory	Abortion at 2 months
3	21	16	5	5	++	0	+	16.2	7.5	Ovulatory	–
4	27	13	14	14	+	6	+	18.5	6.2	Ovulatory	Term
5	26	12	–	14	+	5	0	21.8	6.2	Ovulatory	Term
6	22	13	9	9	+	0	+	20.6	4.5	Ovulatory	–
7	24					5	+	22.0	6.8	Ovulatory	0
8	30	12½	–	17½	+	2½	0	16.3			
9	17	None	Yes	–	+++	0	++	20.0	7.0		–
10	27	13	–	14	+	3	0	15.0	3.2	Ovulatory	Term
11	25	16	9	9	++	0	0	16.3	4.4	Ovulatory	–
12	30	12	–	18	++	0	+	12.3	5.1	Ovulatory	Induced abortion
13	23	14	9	9	+	2	0	12.4	2.9	Ovulatory	0
14	25	14	9	9	++	4	0	16.0	6.3		0
15	31	11	–	7	+	8	0	13.8	6.1	Ovulatory	0
16	30	14	–	16	+	3	0	13.1	6.1	Ovulatory	Term

It is important that the clitoris be extirpated rather than amputated. Erectile tissue remaining as a stump is sometimes painful even under adequate cortisone control.

In a few early cases Young attempted to preserve some clitoral function by transplanting the glands with a flap attached. This was uniformly unsuccessful, due to sloughing.

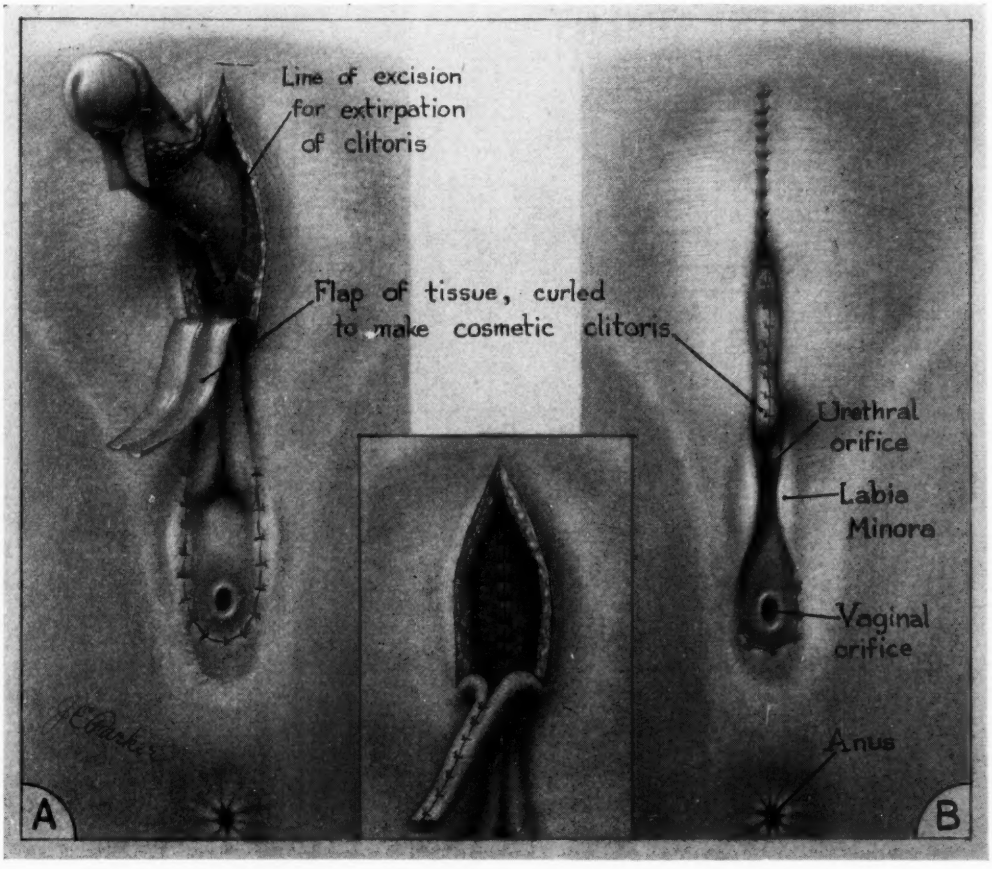


Fig. 13*C*.—*A*, Extirpation of clitoris. (Inset. A different method of construction of the clitoris.)
B, The final situation.

Including the 4 cases first reported by Young, there have been 11 plastic reconstructions of the urogenital-sinus derivatives among 33 clinical Group I, anatomical Group D patients in the years 1934 to 1953. In addition to this, 6 individuals have had a removal of the clitoris without further sinus reconstruction.

Of the 7 cases in clinical Group II, there was one removal of the clitoris and one procedure on the sinus. This is illustrated in Fig. 13 and represents an anatomical situation which should be classed in Group C.

The Gynecological Management of Postpubertal Hirsutism, Oligomenorrhea, and Infertility With or Without Elevated Urinary 17-Ketosteroids—Clinical Groups III and IV

As noted in the section on clinical classification, it cannot be considered certain that clinical Groups III and IV are in fact attenuated forms of classical adrenal hyperplasia. The disorder appears to be closely related, however, for these women present in a diminishing form the classical clinical picture of

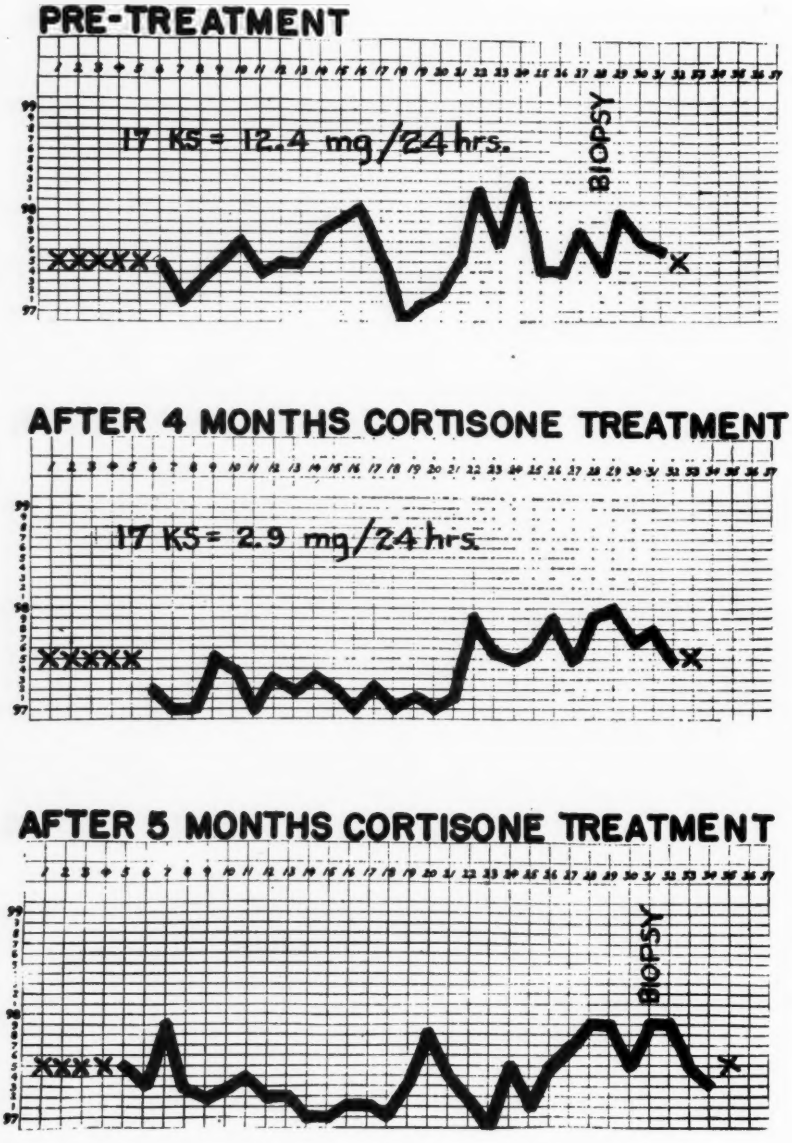


Fig. 14.—*A*, Basal temperature chart of Patient 13 of Table II.

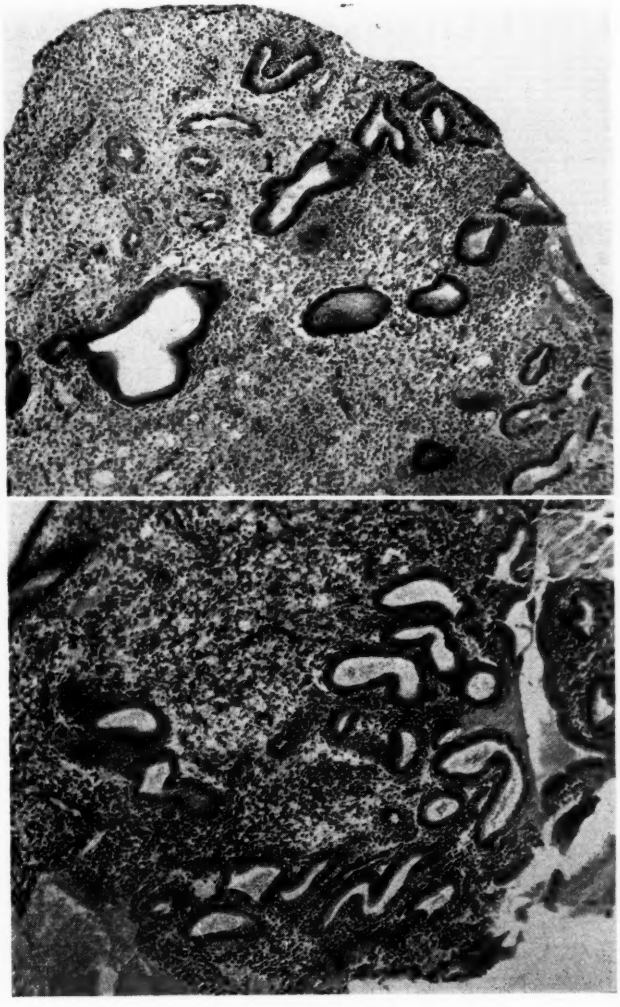
B, Endometrial biopsy on day 28 of 32 day cycle. Pretreatment, showing nonsecretory endometrium.

C, Endometrial biopsy on day 31 of 34 day cycle after five months of cortisone therapy. Secretory endometrium but very poor pattern for the calendar date. Fertility failure probably due to poor luteal function.

adrenal hyperplasia and respond to cortisone in a similar manner; the elevated 17-ketosteroid excretion of patients in Group III argues strongly for the close relationship of this group to the pseudohermaphrodites.

Since patients of Groups III and IV have complaints primarily referable to menstruation and fertility, their care is likely to be undertaken entirely by the gynecologist. All have hirsutism to some degree and this is of varying

B.



C.

Fig. 14, *B, C.—For legend see opposite page.*

concern to individual patients. Clitoral enlargement is never sufficient to consider surgical extirpation but was noted in about half the patients of both Groups III and IV. Either amenorrhea or oligomenorrhea is by definition a part of the syndrome and often, but not always, the menses are anovulatory. When ovulation occurs, poor luteal function is likely to be present as judged

by endometrial biopsies or basal temperature charts. Group III has been separated from Group IV by the level of urinary 17-ketosteroid excretion, which is considered to be elevated if it is above 12 mg. per 24 hours. The details of original findings and therapeutic results of the two groups are recorded in Tables II and III and the behavior of selected cases from these groups is illustrated in Figs. 14, 15, and 16.

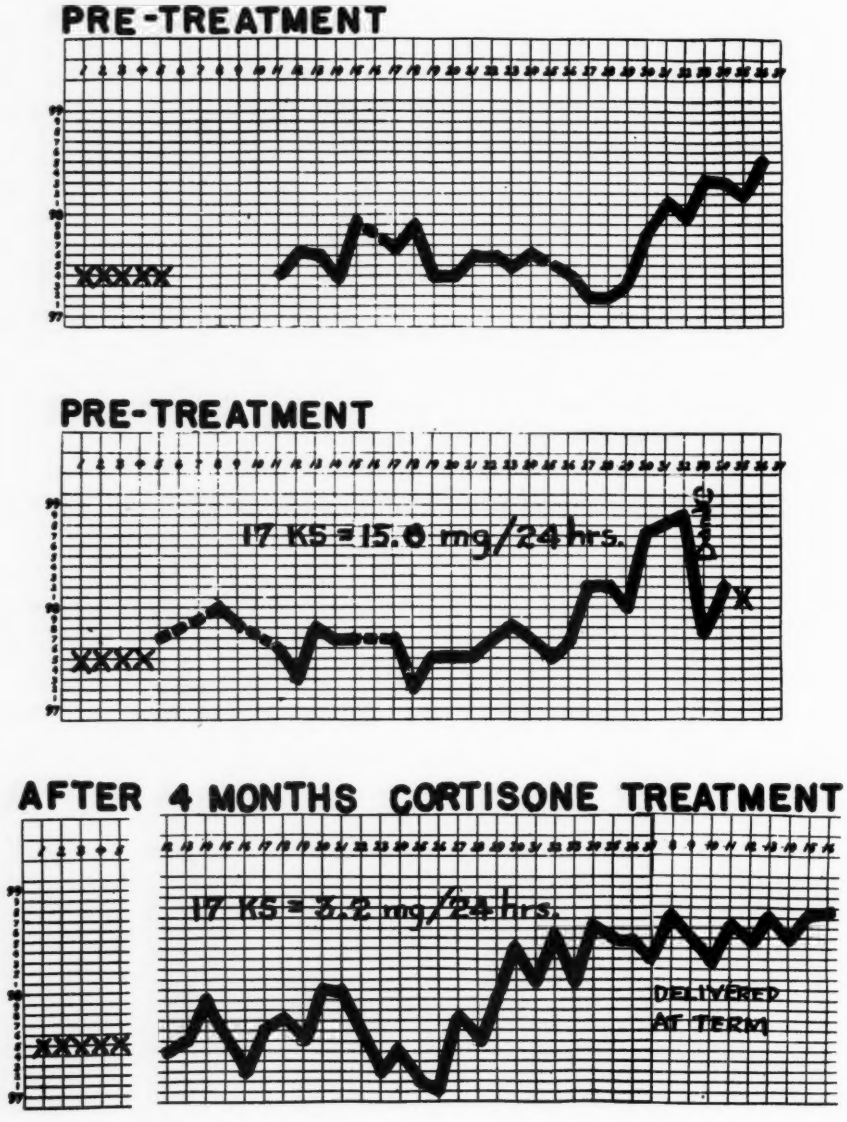


Fig. 15A.—Basal temperature chart of Patient 10 of Table II.

As a rule, cortisone is administered in daily doses of 50 mg. for one month and then reduced to 25 mg. daily. A fall in the 17-ketosteroid excretion occurs regardless of elevation prior to treatment.

As judged by basal temperature curves, ovulation often occurs promptly but good luteal function may require four to six months' therapy.

Hirsutism is seldom favorably affected although some patients have considered that they were improved. This is especially true of the younger age group.

Ovulatory menses are easier to induce than fertility. In Group III pregnancy ensued in 5 of 10 patients who complained of infertility and in Group IV in 7 of 11. Although these groups are too small for statistical evaluation the somewhat better results in Group IV may be another expression of the diminished severity of the disorder in the latter group.

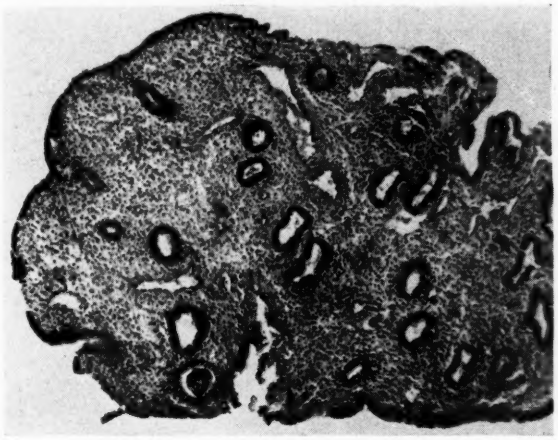


Fig. 15*B*.—Biopsy on day 33 of 35 day cycle showing poor luteal function prior to treatment.

Comment

The observations on the possible steps in the synthesis of cortisone in the normal adrenal,[22] the studies on the urinary steroids in hyperplasia,[5, 6] the blood ACTH levels,[2] and the pathological studies of adrenals and ovaries allows one to speculate on the pathogenesis of the adrenal hyperplasia syndrome. The working hypothesis detailed hereafter is based upon that of Wilkins.[24]

It has been shown by perfusion of beef adrenals that cortisone may be derived by perfusing adrenals with 17-hydroxyprogesterone. If there is a defect in utilizing this substrate, it might be expected to accumulate and serve as a source for the urinary pregnanetriol, which has been reported by Bongiovanni and others to be elevated.

Pathological examination of diseased adrenals has shown an anatomical and functional defect in the fascicular layer of the cortex. The fascicular layer has been implicated in the production of glucocorticoids, i.e., cortisone. This defect may be viewed as the primary fault in this condition.

Cortisone is apparently the steroid which suppresses pituitary ACTH production. The absence of this compound in the diseased state allows an overproduction of ACTH, which is able to stimulate only the reticularis, as the

fascicular layer is defective. The hyperplastic reticularis is probably the site of the virilizing compound which may suppress pituitary gonadotrophes and be the precursor of the abnormal urinary 17-ketosteroid.

The study of ovarian pathology indicates that FSH is present in amounts sufficient to cause the production of antrum follicles. Furthermore, urinary FSH determinations in three patients of Group II showed values within normal limits for menstruating women. As reticular hyperplasia progresses, however, FSH may be suppressed as indicated by absence of follicles in the ovaries of pseudohermaphrodites in the older age group.

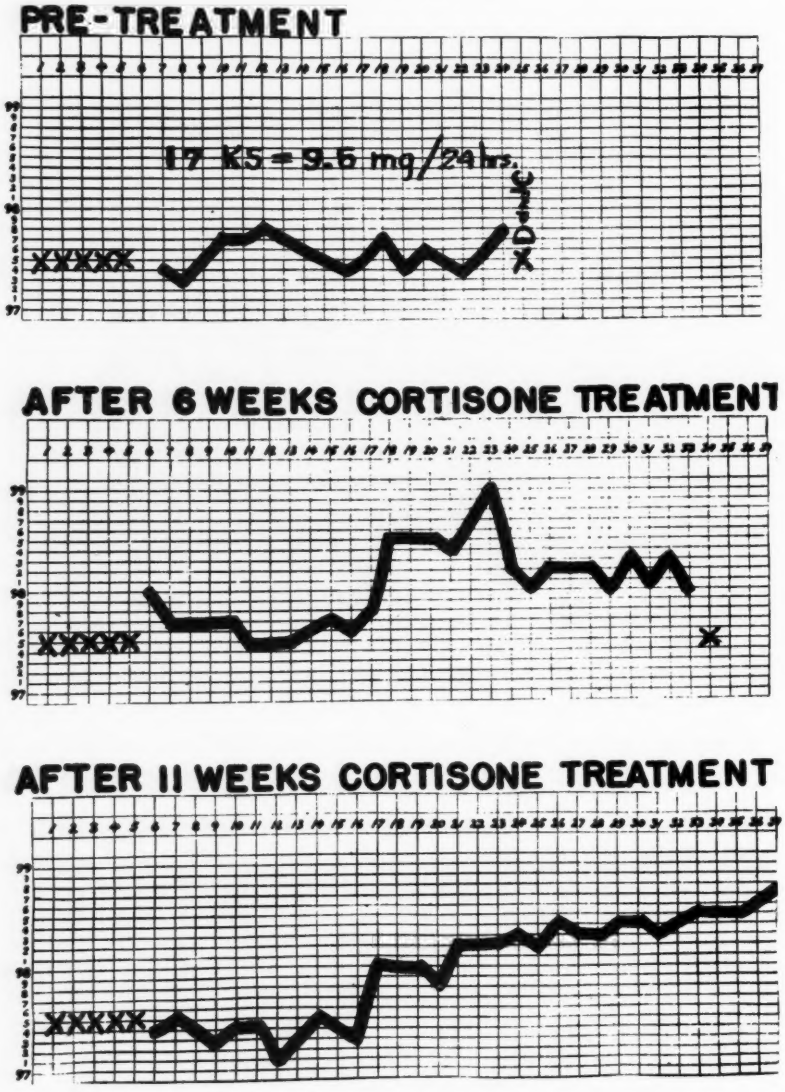


Fig. 16A.—Basal temperature chart of Patient 13 of Table III.

The failure of ovulation would imply an interstitial cell stimulating hormone deficiency. This was substantiated in two patients of Group II, as no urinary ICSH was detectable by the McArthur method.

Luteotrophin might also be deficient in view of the poor luteal function and observations are required on this point. It is possible, however, that inadequate ICSH would be sufficient to explain the poor luteal function as ICSH is considered necessary in the laying down of precursor substance for the production of progesterone.[25]

The administration of cortisone, therefore, may be viewed as substitution or replacement therapy for a defective adrenal fasciculata function. Its action is to suppress ACTH and thereby the androgenic production of the reticularis. The diminution of these reticular steroids in turn allows the domination of ICSH with its accompanying ovarian effects of estrogen production and ovulation.

If such a theory does approximate the facts, it can explain the very prompt ovulation which occurred in some patients with the attenuated form of the disease.

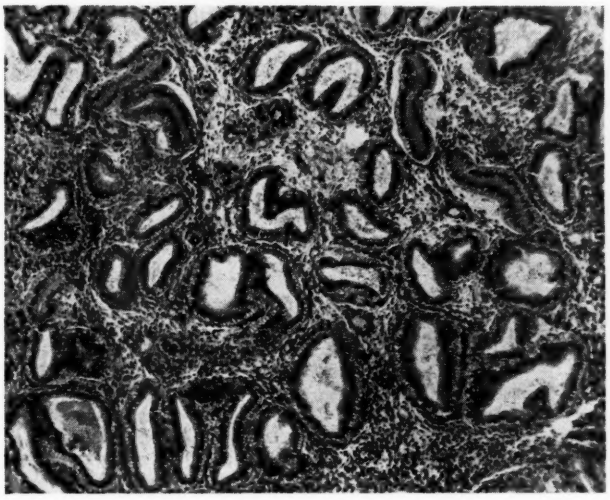


Fig. 16*B*.—Endometrial biopsy on day 24 showing poor secretory activity.

Summary and Conclusions

1. The gynecological aspects of four series of patients with congenital adrenal hyperplasia or an allied disorder are presented. These vary from classical female pseudohermaphroditism to individuals with hirsutism, oligomenorrhea, and infertility.

2. The adrenal changes in fifteen patients with adrenal hyperplasia are described. The glomerulosa and fasciculata are either anatomically absent or devoid of lipid, and the reticularis is very hyperplastic and contains large quantities of lipid.

3. The ovaries of seventeen individuals with adrenal hyperplasia were examined. With progressing age there is a gradual failure of normal follicular growth. Evidence of ovulation was not observed.

4. The developmental anomalies of the genital tubercle and urogenital sinus are depicted.

TABLE III. CLINICAL DATA OF PATIENTS IN GROUP IV

PATIENT	AGE	AGE AT MENARCHE	YEARS OF AMENORRHEA	YEARS OF OLIGOMENORRHEA	DEGREE HIRSUTISM	YEARS OF INFERTILITY	DEGREE CLITORIS ENLARGEMENT	17-KETOSTEROIDS		RESULT	
								BEFORE CORTISONE	AFTER CORTISONE	MENSES	FERTILITY
1	26	13	13	–	+	5	0	9.6	4.2	Ovulatory	Abortion
2	20	11	6	–	+	0	0	4.8	2.3	0	–
3	29	11	–	13	+	7	0	5.9	–	Ovulatory	Abortion at 2 months
4	22	13	11½	1½	+	0	0	8.0	3.1	Ovulatory	–
5	20	13	–	7	++	3½	+	6.5		Ovulatory	0
6	20	12	–	8	++	0	+	5.0		Ovulatory	–
7	28	11	–	17	+	2	0	6.8		Ovulatory	0
8	27	13	14	14	++	2	0	8.8	2.9	Ovulatory	Abortion
9	19	12	4	4	++	0	0	7.6	3.5	Ovulatory	–
10	28	13	15	–	++	4	+	5.4	5.5	Ovulatory	0
11	29	12	12	–	+	11	+	4.8	–	Ovulatory	Term
12	28	12	16	16	+	5	0	5.1	2.5	Ovulatory	Term
13	30	13	–	17	+	1½	+	9.5	7.1	Ovulatory	Term
14	32	12	–	8	++	4½	+	6.1	5.7	Ovulatory	Term
15	20	14	6	6	++	1½	+	11.6	4.4	Ovulatory	0

5. The surgical reconstruction of the external genitals in individuals with severe anomalies is presented.

6. The result with cortisone therapy in 31 women with postpubertal hirsutism, oligomenorrhea, and infertility is presented.

We are indebted to Dr. Arnold Rich and the Department of Pathology, Dr. Lawson Wilkins and the Department of Pediatrics, and Dr. William Scott and the Department of Urology for access to material and records within their departments.

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Discussion

DR. E. STEWART TAYLOR, Denver, Colo.—One can hardly suggest a medical or pediatric problem of obscure etiology that has not been treated with cortisone on the basis of reason or empiricism. I think now, notwithstanding a slow start, you have heard from Dr. Jones a preview of very important developments in endocrinology that may provide insight into such baffling problems as functional amenorrhea, oligomenorrhea, hirsutism in the female, and infertility. You may be certain that the pharmaceutical houses and their agents will not fail to see the implications of cortisone in gynecology, and I predict a rush for cortisone for everything of gynecologic nature.

Dr. Jones has invited our attention to his suggestion that hyperfunction of the adrenal cortex appears as a clinical entity in a range of circumstances varying from severe to mild. It is an established fact that congenital adrenal cortical hyperplasia produces the androgenital syndrome in the female (female pseudohermaphroditism). This disease process and its effects on the subject can be partly reversed by cortisone. We have 4

such patients in our own clinic, and all have had amazing changes of virilism to feminism after cortisone treatment. Each of these patients had elevated 17-ketosteroid levels that were brought to physiological levels by cortisone treatment.

A second established syndrome that Dr. Jones has presented is his second group known as acquired adrenal cortical hyperplasia resulting in virilism. The 17-ketosteroids are elevated, the patient has hirsutism, an enlarged clitoris, and amenorrhea. Those organs ordinarily stimulated by estrogen are atrophic, while those stimulated by androgen are hypertrophied. Cortisone treatment has produced menstruation and tended to reverse the adverse virilism. We have one such patient who has been on cortisone treatment for eight months. Menstruation has not occurred, but the breasts have enlarged slightly, the body hair has become more fine in texture, and the 17-ketosteroid level promptly fell to normal and has remained so.

These two groups of patients are rare and will not be encountered in large numbers by many gynecologists.

Dr. Jones' last two groups, although not yet clearly identified as syndromes related to mild adrenal cortical hyperplasia, represent a larger fraction of gynecologic practice. Any theory or practice that advances our knowledge concerning amenorrhea, hirsutism, or infertility is most welcome. Groups III and IV are somewhat puzzling, particularly IV. The inhibition of 17-ketosteroid output in Group III with oral cortisone, especially with a dosage of 50 mg., is considerably greater than that ordinarily seen when normal adrenals are so exposed. This in itself suggests that these adrenals may be abnormal. If so, the response to therapy is both gratifying and not entirely unexpected. In the 16 patients from the group characterized by postpuberty hirsutism, oligomenorrhea, and infertility with elevated 17-ketosteroids, all 16 had a fall in 17-ketosteroid levels while taking cortisone, and all developed ovulatory menses. Five of 10 patients in this group who complained of infertility became pregnant. We have 2 patients who had elevated 17-ketosteroids and long-standing amenorrhea before treatment with cortisone. These patients have been on cortisone treatment for four months and menstruation has occurred, but there have been no pregnancies.

It should be mentioned that there are many hirsute females with moderately elevated 17-ketosteroid excretion who for one reason or another get no reduction in 17-ketosteroids after cortisone treatment. In these patients there has been no explanation of the relative masculinization signs.

Dr. Jones' last group of patients numbered 15. They were in all ways similar to the previous group of 16 except that the 24 hour excretion of 17-ketosteroids was not elevated. Cortisone was used nevertheless and the ovulatory menstruation exhibited by 14 of the 15 is an impressive clinical response to cortisone. Seven patients of this group became pregnant. In the combined series, I am impressed by the occurrence of 13 pregnancies with practically half ending in abortion. Does the adrenal gland have something to do with abortion? Since the 17-ketosteroid levels were not elevated in this last group of patients one wonders what the relationship of the results is to abnormal androgen secretion. It is more difficult here to believe that the menstrual response is the result of cortisone on the adrenal cortex. It is difficult to understand why the resting 17-ketosteroid (androgen) output or the effect of cortisone on 17-ketosteroid excretion is directly related to the original complaints or to the effects of therapy.

Dr. Jones has enlarged the work of Blackman which attempts to localize the abnormal metabolism of the masculinizing sex hormone of the reticular zone of the adrenal cortex. Certain of the evidence is strongly in support of this. There are those, however, who disagree with the general conclusion. The authors have recognized the difficulty of labeling the zones of the adrenal cortex by staining methods related to specific zonal steroid secretion. One might point out that hyperplasia of the adrenal cortex, which is histologically indistinguishable from adrenal hyperplasia producing virilism, may cause Cushing's syndrome instead of virilism. Likewise, we should remember that there have been numerous attempts by pathologists and gynecologists to correlate clinical findings of adrenal rest

tumors of the ovary with microscopic findings. Microscopic criteria have uniformly failed in this respect. One cannot tell from histologic examination of a given adrenal cortical tumor from the suprarenal area or from the ovary whether the metabolic effect of the tumor on the patient will be that of virilism, Cushing's syndrome, or a mixture of the two. Dr. Jones has by histochemical means helped to localize the pathologic physiology of adrenal virilism.

The ovarian changes described are those that might be expected in an ovary long suppressed by excess androgens. Follicle-stimulating hormone is the last function to be eliminated by the excessive androgen from the adrenal cortex. It also is the first of the pituitary hormones influencing the ovary to become effective when cortisone is used for the correction of adrenal cortical hyperfunction. Sofer suggested that cortisone administration increased FSH output, and it has been suggested that LH (ICSH) may partially control adrenal androgen secretion. The evidence for LH control of the adrenal is actually poor; this does not, however, indicate that adrenal androgens may not influence LH. There is little information concerning the effect of cortisone on LH.

It is interesting to note that the treatment of choice for adrenal hyperplasia that causes virilism is medical, whereas the adrenal hyperplasia associated with Cushing's syndrome is essentially a surgical disease.

I think that the Jones family has modestly and significantly added to our knowledge of adrenal hyperfunction as it may exist in milder forms than outright adrenal virilism, and has made important additions to the histopathology of adrenal hyperplasia.

DR. RUSSELL R. DE ALVAREZ, Seattle, Wash.—This magnificent report of the Drs. Jones represents the largest number of cases recording the histopathology of adrenocortical hyperplasia. While the basic defect in adrenal cortical function causing the syndrome of adrenocortical hyperplasia and the adrenogenital syndrome has not yet been clarified, it is agreed that the anterior pituitary secretes excessive amounts of ACTH. The adrenal cortex responds—the Joneses show us that it is the reticularis—with an increased output of steroids, primarily androgenic in type, resulting in a markedly increased urinary output of 17-ketosteroids. The output of estrogen and "pregnandiol" is also increased, but the excretion of corticoids (glucocorticoids) is not increased; if anything, it is reduced.

Although patients with adrenocortical hyperplasia respond to ACTH administration with a further increase in 17-ketosteroid output, Bartter and Albright report that they show insignificant increases in the excretion of reducing steroids (glucocorticoids). It was, therefore, suggested that the adrenal cortex was unable to synthesize the glucogenic corticoids (Compound F). Because of this, compensatory efforts of the pituitary resulted in the secretion of excessive amounts of ACTH. The increased elaboration of ACTH then overstimulated the adrenal cortex in an attempt to bring about an increased output of glucogenic corticoids, but, in so doing, an excessive production of androgen also occurs because of the excessive degradation of glucocorticoid synthesis to 17-ketosteroids. A defect occurs at the 17-hydroxyprogesterone step in the synthesis of Compound F, by the formation of pregnanetriol, a metabolite of 17-hydroxyprogesterone. Just as the formation and excretion of 17-ketosteroids are inhibited by cortisone therapy, so is the excretion of pregnanetriol similarly decreased. When pregnanetriol is present, although in itself nonvirilizing, it seems to indicate a primary adrenocortical virilizing defect. Its determination would be singularly helpful among those patients whose excretion of 17-ketosteroids is within the limits of normal. In order to justify the inclusion of Dr. Jones' Group IV cases, it would seem desirable to ascertain whether or not tests for the detection of pregnanetriol were performed on this group of patients, whose inclusion as cases of adrenal hyperplasia might be questioned.

When cortisone or Compound F is administered exogenously, the body needs for corticoids are supplied, the anterior pituitary output of ACTH is inhibited, and stimulation of the adrenal cortex ceases. Therefore, the output of androgens decreases sharply, virilization is reversed, and normal anterior pituitary-ovary interrelationships are established.

DR. EMIL G. HOLMSTROM, Salt Lake City, Utah (By invitation).—When I noted on the program that there was a discussion scheduled on pseudohermaphrodism, I could not resist bringing along some slides illustrating some patients we have treated. We have had to meet a different problem in regard to 2 patients. Both were raised as boys until the age of 5 at which time it was recognized that they were girls. It was decided to give both of them cortisone to cut down their metabolic growth. It is known that in the absence of cortisone treatment most of these children will end up as dwarfs, even though for a time they are "little giants." Under cortisone therapy both of these patients began to have menstrual periods. Then the decision had to be made as to whether something should be done to prevent the occurrence of bleeding or whether cortisone should be discontinued. The pediatricians felt that cortisone should be continued, and the parents felt that they could not make the adjustment if these individuals were to be regarded as females. It was, therefore, decided to perform hysterectomies and salpingo-oophorectomies on them. I am not sure that this decision would be acceptable to all of you. I would like to show pictures of these patients, primarily to emphasize my plea for a more accurate diagnosis as to sex at the time of birth. The sex was erroneously determined at birth in both these cases and they were raised as boys.

The first child was 4 years of age when cortisone therapy was instituted. On this therapy his excretion of 17-ketosteroids dropped to almost normal whereas it had previously been high. This child has a urogenital sinus and it has been demonstrated that there is a vagina which communicates with the urethra. Under cortisone therapy he has developed along normal patterns. After three years of cortisone therapy vaginal bleeding began. The decision was made that he should continue as a boy, that it was too late to change him into a girl, so removal of the internal genitals was carried out.

The second child presented a similar problem. This child was thought to be a male. A urologist had on three occasions attempted to correct the hypospadias without realizing the child was really a female. You can see on this slide that the operations were partially successful in that the meatus is part way up on the shaft of the phallus instead of at the base. You can also notice beginning breast development under cortisone therapy. Menstrual bleeding occurred. It was then decided to remove the internal genitals. The organs removed were so normal that we use them as demonstration specimens.

We have seen one patient who was more fortunate. A correct diagnosis was made shortly after birth. She has been on cortisone therapy, is now 4 years of age. Recently the enlarged clitoris has been removed but we have done nothing more since we thought it would be better to wait until she was older to do the plastic procedure on the vagina.

I wish to ask Dr. Jones at what age he recommends that the plastic procedures on the genitals be carried out.

DR. EDWARD C. HUGHES, Syracuse, N. Y. (By invitation).—I wish to present two cases that emphasize the importance of Dr. Jones' excellent presentation.

The first slide is a picture of a 7-year-old twin, who was referred to the endocrine service of our department under the direction of Dr. Charles Lloyd. Her mother noted that she had grown considerably taller than the sister, that there was hirsutism of the pubis and an enlarged clitoris. Laboratory examinations showed that the 17-ketosteroids were elevated 12 to 20 mg. per 24 hour urine specimen and that the total corticosteroid excretion was elevated to 0.3 mg. per 24 hour specimen. We suspected adrenocortical hyperplasia. Both adrenals were explored grossly and microscopically; they were found to be hyperplastic. The clitoris was extirpated and the patient put on cortisone, 50 mg. per day. Her 17-ketosteroids decreased to normal (0.1 mg.) level. She was maintained for two years on cortisone. Three weeks ago she developed measles with high fever. As a result she developed adrenal insufficiency and died. I think it should be emphasized that any patient who is on cortisone may develop adrenal insufficiency if severe infection with fever intervenes and needs prompt treatment with increased doses of cortisone.

The next case was similar. This 7-year-old had grown more than she should have and she also had an enlarged clitoris. The 17-ketosteroids of 70 to 90 mg. per 24 hour urine specimen and her total corticosteroids of 0.4 mg. per 24 hour specimen were high. An adrenal tumor was suspected; she was operated upon and an adrenal adenoma was found and removed. Postoperatively the 17-ketosteroids decreased to normal levels. She is now well. Extraction of the steroid from the tumor and evaluation by paper chromatography showed a steroid which resembled that found in the urine of this patient. It was chromatographed at the same location as that identified as Compound F.

DR. HOWARD W. JONES, JR. (Closing) (By invitation).—Dr. Taylor has pointed out the fact that Group IV is extremely debatable, and Dr. de Alvarez has asked about the pregnanetriol excretion in that group. We have been interested in urinary pregnanetriol, but did not feel that the data up to the present were sufficient to include in this paper. Pregnanetriol excretions have been done on one case from Group III and in that instance was elevated; in 2 patients from Group IV who had been under treatment with cortisone, it was not elevated. There were 3 untreated cases in the group in which it was elevated.

Dr. Taylor mentioned that some individuals fail to have a response to cortisone by lowering their 17-ketosteroid levels. Under those circumstances, the possibility of an adrenal tumor is to be considered. Venning and others have suggested that failure of urinary 17-ketosteroid depression after cortisone as a possible test for tumor. The other possibility is that the patient is not taking the cortisone, and under those circumstances it might be well to administer it parenterally because, in our experience, it is unusual to fail to get diminution of the 17-ketosteroids with cortisone.

Dr. Taylor also mentioned the confusion which exists because of the labeling of Cushing's disease and the adrenogenital syndrome as due to hyperplasia of the adrenals. We would not agree that the histologic findings in the adrenals in these syndromes are similar, unless one confines his remarks to the zona reticularis which may be hyperplastic in either syndrome. The principal difference is in the fasciculata which in the adrenogenital syndrome is absent anatomically or functionally as far as lipid content is concerned, whereas in Cushing's disease it may appear normal or actually hyperplastic.

I might be able to comment on Dr. de Alvarez's remarks as to the possible mechanism of action: We note the zona fasciculata giving rise to cortisone and the zona reticularis giving rise to androgen. Normally a balance exists between the output of the fasciculata and ACTH so that cortisone will suppress ACTH. In adrenal hyperplasia the fasciculata is deficient and there is no suppression of ACTH which attempts to stimulate the fasciculata but, being deficient, the latter cannot respond by producing cortisone. The reticularis is normal, however, and has the capacity to respond and becomes hyperplastic, producing androgenic substances responsible for virilization of the patient and suppressing pituitary gonadotropins which do not then stimulate the ovaries. If we may consider the ovary of patients with adrenal hyperplasia as a test object, we conclude that there is adequate FSH and that there is some suppression of ICSH or an interference of the proper FSH/ICSH ratio.

Dr. Holmstrom asked about the age for correction of anatomical defects. If one eliminates those patients who have other serious metabolic defects, we have now come to believe that the earlier they are corrected the better. The youngest patient we have operated upon was 18 months of age, and it was very easy to do. Therefore, we see no reason to postpone the operative procedure, although this cannot be settled until time has elapsed to know whether there are problems with contraction of the newly formed outlet.

Dr. Hughes' patient is very important because there is no disease in one twin. Adrenal hyperplasia has a tendency to occur in sisters, and in Dr. Wilkins' group there are about 5 pairs of sisters with this disorder. If it occurs in only one twin, one can eliminate the possibility of maternal environmental factors and is obliged to go back to more fundamental genetic relationships.

EPIPHYSEAL MATURATION IN THE NEWBORN AS RELATED TO MATERNAL NUTRITIONAL STATUS*

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(From the Pennsylvania Hospital [Philadelphia Lying-In Hospital], Nutrition Research Clinic†)

THE factors affecting the sequence and time of appearance of the various epiphyseal centers in the newborn are not known. Wide individual variation in the absence or presence of specific centers at birth, as well as in the size of the centers present, has been noted by previous investigators. More than 30 years ago, a number of investigators[1] attempted to estimate the fetal age by examining for stage of development of centers of ossification but lack of constancy in these centers led to the conclusion that no single center, or any combination, gave a reliable index of fetal age. To the present time, there has not been any clarification of the prenatal factors which may influence the maturation of centers which typically appear at or near term.

Since the Nutrition Research Clinic was concerned with the effects of the maternal nutritional status on the status of the infant at birth, it was decided that an evaluation of the effect of maternal status during pregnancy on the character, sequence, and time of appearance of certain epiphyseal centers might furnish new and useful data on this question. In general, growth is associated with the availability of essential nutrients, and it seemed possible that these nutrients would affect the growth-stimulating mechanism involved in skeletal development. Consequently, we have been interested in whether or not variations in levels of these nutrients could be shown to alter the rate of maturation of selected growth centers. The study was designed in such a way that an evaluation could be made of the maturation of the epiphyseal centers in the knee and heel by means of x-rays. The x-ray technique used was that outlined by the Growth Study Center of the Pennsylvania State College.

The babies x-rayed were an unselected series of over 300 born at term, i.e., babies weighing 5.5 pounds or more at birth, except for three babies of 39 weeks' gestation that weighed 5 to 5.5 pounds. The data to be presented are related to the epiphyseal centers of the knee and heel using the epiphyseal center at the distal end of the femur, the proximal end of the tibia, and the os calcis. When these centers were present the vertical and transverse measurements were made in millimeters.

The population and procedures of the Nutrition Research Clinic were as follows: All prenatal patients who registered at the Philadelphia Lying-In

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Hospital were referred to the Nutrition Research Clinic if the estimated duration of gestation was not more than sixteen weeks, if the patient was married, and if there was no indication of serious chronic disease or syphilis,* unless the patient refused to attend clinic in the afternoon. With these exceptions, the patients were an unselected series from the ward service of the hospital.

Patients registered in the Nutrition Research Clinic were assigned seriatim to one of four study groups by the statistical staff in a manner which would maintain comparability among the four groups for race, age, and gravidity of patients. The four primary study groups were as follows:

A. Control group, no supplement.
B. Vitamin supplemented group.†
C. Protein supplemented group.†
D. Vitamin and protein supplemented group.

Patients in all groups received throughout their pregnancies the same prenatal care and management. Diet instructions were given by the nutritionist and supported by supervision and direction of the obstetric staff of the clinic. The diet used in the research study was marginal and designed to produce a base line against which supplementation could be expected to show a differential, if such a differential existed.

It must be pointed out that the maintenance of patients on a marginal dietary intake, to which known amounts of supplements are added, is specifically for the purpose of evaluating the needs for the specific nutrients added. It is not intended to infer that this procedure represents a desirable method of obtaining an optimum nutritional status.

Race and Sex Differences at Birth

Since differences in degree of maturation at birth by sex and also by race have been reported, a description of the differences found for this population is presented.

Fig. 1 (Table I) is based on all babies x-rayed within the first five days after birth; and for the centers indicated shows the percentage that was absent at the time of the observation. The difference in maturation of the os calcis is statistically significantly different by both race and sex. It is of interest to note that the white male babies had a striking incidence of delayed maturation as indicated by the time of the appearance of the os calcis. It is generally considered that Negro patients have a less favorable response to stress than do other patients, yet it appears that the rate of maturation during the intrauterine period is more rapid in the Negro baby than in the white infant.

The lower half of Fig. 1 indicates the absence or presence to 1 to 2 mm. of the epiphyseal center at the proximal end of the tibia. Here it is obvious

*Patients with chronic disease or syphilis referred to the Nutrition Research Clinic were carried but have been excluded from tabulations in this report. Chronic diseases excluded are essential hypertension, chronic heart disease classified II-a or higher, chronic nephritis, and chronic pyelitis.

†The nutrient supplements used in this study are: Polyvitamin concentrate (Upjohn's Zymacaps), three capsules per day; protein concentrate (Mead Johnson & Company's Protenum), to furnish 50 Gm. of protein daily if taken as advised.

TABLE I. MATURATION OF EPIPHYSEAL CENTERS IN THE KNEE AND HEEL AT ONE TO FIVE DAYS AFTER BIRTH BY RACE AND SEX*

OSSIFICATION CENTER RACE AND SEX	TOTAL	CENTER ABSENT	SIZE OF CENTER (MM.)					PER CENT BY SIZE OF CENTER						
			1-2	3-4	5-6	7-8	9+	TOTAL	ABSENT	1-2	3-4	5-6	7-8	9+
Heel, total	304	145	42	48	64	5		100.0	47.7	13.8	15.8	21.1	1.6	0
White male	114	68	17	12	16	1		100.0	59.6	14.9	10.5	14.0	0.9	0
White female	90	42	11	13	23	1		100.0	46.7	12.2	14.4	25.6	1.1	0
Negro male	54	21	9	15	7	2		100.0	38.9	16.7	27.8	13.0	3.7	0
Negro female	46	14	5	8	18	1		100.0	30.4	10.9	17.4	39.1	2.2	0
Tibia, total	315	65	41	44	76	63	26	100.0	20.6	13.0	14.0	24.1	20.0	8.3
White male	117	30	11	22	27	18	9	100.0	25.6	9.4	18.8	23.1	15.4	7.7
White female	94	11	17	8	27	20	11	100.0	11.7	18.1	8.5	28.7	21.3	11.7
Negro male	55	14	7	10	12	10	2	100.0	25.5	12.7	18.2	21.8	18.2	3.6
Negro female	49	10	6	4	10	15	4	100.0	20.4	12.2	8.2	20.4	30.6	8.2
Femur, total	314	4	9	36	119	120	26	100.0	1.3	2.9	11.5	37.9	38.2	8.3
White male	117	2	2	20	43	41	9	100.0	1.7	1.7	17.1	36.8	35.0	7.7
White female	93	0	2	7	30	47	7	100.0	0	2.2	7.5	32.3	50.5	7.5
Negro male	55	0	5	6	25	15	4	100.0	0	9.1	10.9	45.5	27.3	7.3
Negro female	49	2	0	3	21	17	6	100.0	4.1	0	6.1	42.9	34.7	12.2

*Babies weighing 5.5 pounds or less at birth are excluded if the estimated period of gestation was less than 39 weeks.

that there is considerably less difference than was observed relative to the os calcis; and the differences by race are not significant. By sex, however, there is a borderline statistically significant difference between the white males and the white females (P = .05). Although the Negro baby demonstrates the same pattern as was observed for the os, the difference is much less and is not statistically significant.

FIG. 1 OS CALCIS AND TIBIAL EPIPHYSEAL CENTERS — PER CENT ABSENT AT BIRTH

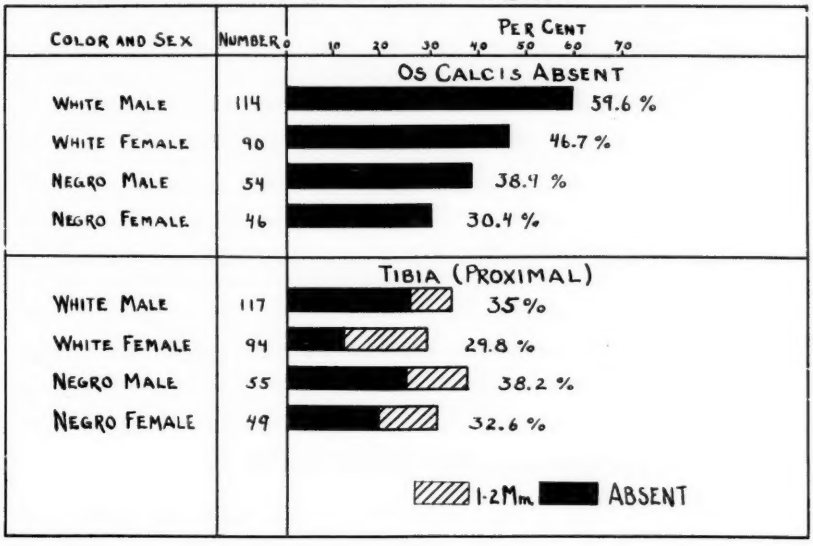


FIG. 2 DISTAL EPIPHYSEAL CENTER OF FEMUR TRANSVERSE MILLIMETER MEASUREMENT

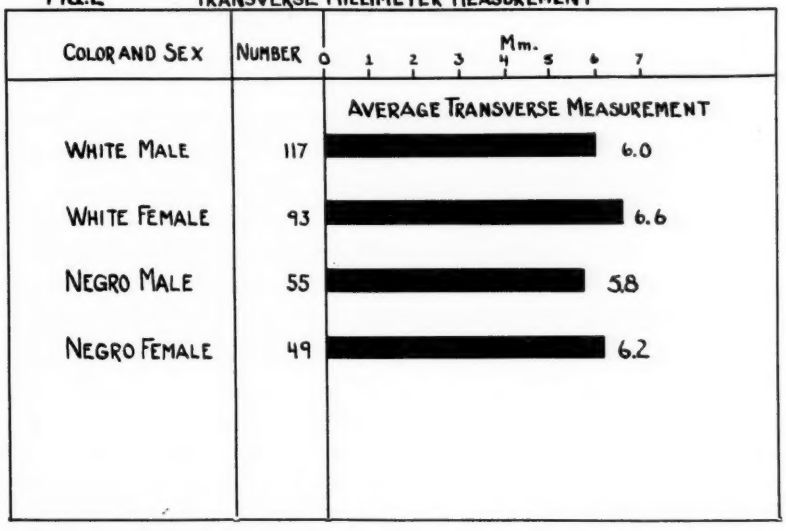
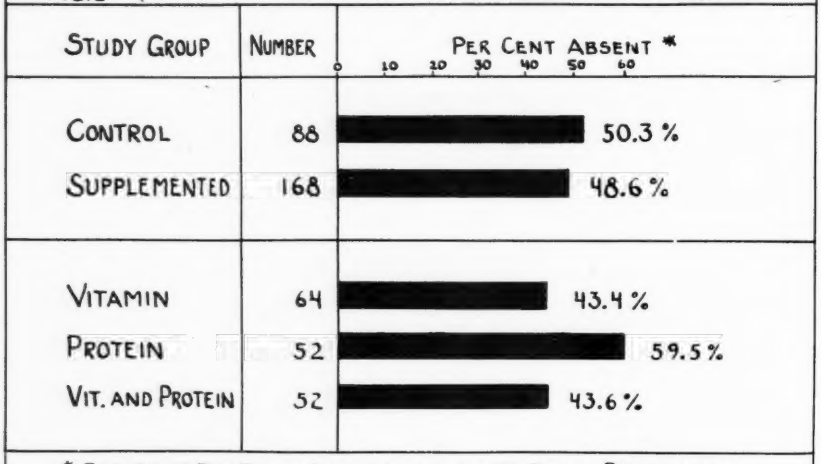


Fig. 2 considers the epiphyseal center at the distal end of the femur; and the transverse measurement in millimeters is indicated. It is evident that maturation of this center is well advanced at the time of delivery. The difference in size between the white and Negro babies is not significant. There is,

however, a statistically significant difference by sex for the white babies, the male babies having a significantly smaller average transverse measurement than do the females. Although the sequence of appearance of the femur is further ahead, and much better developed than the other two reported centers, the pattern remains the same.

In a problem as fundamentally biologic as growth it appears that there are dominant factors operating which are associated with sex. A racial difference also is shown which is not evident in relation to time of appearance of the center. Thus, the os calcis, which is absent at birth in about one-half the white babies, is absent in only one-third of the Negro babies. The center at the distal end of the femur, however, which is nearly always present and has gone through its early development, shows only a slight difference in size by race. It is of interest that in a study of ossification centers in the wrists of white and Negro babies, Hess[2] found centers present in 28 per cent of the Negroes and 16 per cent of the whites.

FIG. 3 OS CALCIS – PER CENT ABSENT ACCORDING TO STUDY GROUPS



* PER CENT FOR EACH GROUP ADJUSTED TO EQUAL PROPORTIONS BY COLOR AND SEX

Supplementation and Maturation

In previous reports it has been shown that supplementation during pregnancy is associated with an improved maternal status. It has also been shown to be related to an improvement in infant status as reflected by a lower incidence of prematurity. It is, therefore, of interest to consider the effect of maternal supplementation during pregnancy on the efficiency of the growth-stimulating mechanism in the fetus. On the basis of our previous experience it might be expected that one of the criteria of benefits to patients taking nutritional supplements would be an improvement in the maturation process.

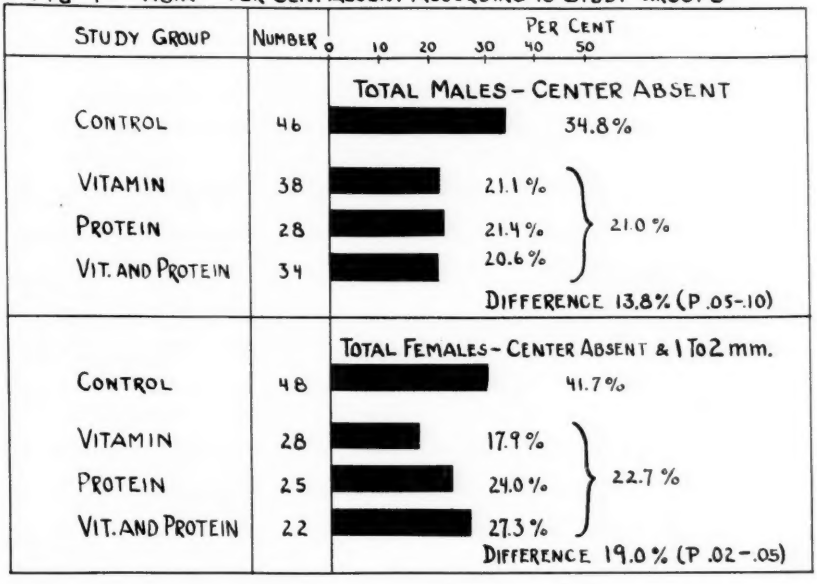
In Fig. 3 is shown the per cent of newborn infants in whom the os calcis was absent according to the four study groups.* It was shown that for all cases studied the os calcis had not yet appeared in approximately 50

*In the analysis by study groups, babies of patients who received the protein supplement have been included only if the mother received at last one-half the planned amount of protein.

per cent of the cases. Obviously, the formative stage of the absent centers is unknown, and absence of the center is not a complete or sensitive index of possible delay in the developmental process. Although there are slight differences in the maturation process among the supplemented groups, a statistically significant difference did not occur.

Fig. 4 considers the epiphyseal center at the proximal end of the tibia. Here the per cent of male babies with the center absent, and the per cent of female babies with the center absent or at 1 to 2 mm.* is shown among the four study groups. It would appear that a mature baby delivered at term should have this epiphyseal center present at birth, and that it is a more sensitive index of the maturation process than are the other centers observed. Some effect of maternal supplementation is reflected in the tibial epiphyseal center of the knee. In all three supplemented groups there were a smaller number of babies, both male and female, with delayed maturation than occurred in the control group. When the three supplemented groups are combined the difference is statistically significant among the female babies, but is not significant for the male babies.

FIG 4 TIBIA – PER CENT ABSENT ACCORDING TO STUDY GROUPS



In Fig. 5 the progress of maturation of the epiphyseal center at the lower end of the femur is shown for the four supplemented groups. This is demonstrated in two ways: the averages for the transverse dimension in millimeters and the per cent of infants with delayed maturation. In the upper half of Fig. 5 the transverse measurements for the control and supplemented male and female babies are shown. In the lower half is indicated the per cent of delayed maturation among the male and female babies for the control and supplemented groups. Although the pattern indicates a slightly more advanced growth of this center among the supplemented groups, there is not any significant difference either in the average size or in the percentage with retarded development.

*The per cent absent or present at 1 to 2 mm. in size for female babies is approximately the same as the per cent absent for male babies.

TABLE II. MATURATION OF EPIPHYSEAL CENTERS IN THE KNEE AND HEEL AT ONE MONTH AFTER BIRTH BY RACE AND SEX

	NO. OF CASES WITH SPECIFIED READING AT 1 MO.							PER CENT OF TOTAL							
	TOTAL	BLANK	1-2	3-4	5-6	7-8	9-10	11+	TOTAL	BLANK	1-2	3-4	5-6	7-8	9-10	11+
Os, total	147	23	7	35	59	22	1	0	100.0	15.6	4.8	23.8	40.1	15.0	0.7	0
White male	51	8	4	20	15	4	0	0	100.0	15.7	7.8	39.2	29.4	7.8	0	0
White female	36	6	1	7	16	6	0	0	100.0	16.7	2.8	19.4	44.4	16.7	0	0
Negro male	31	6	0	2	14	8	1	0	100.0	19.4	0	6.4	45.2	25.8	3.2	0
Negro female	29	3	2	6	14	4	0	0	100.0	10.3	6.9	20.7	48.3	13.8	0	0
Tibia, total	146	3	7	7	21	40	48	20	100.0	2.0	4.8	4.8	14.4	27.4	32.9	13.7
White male	49	2	3	2	4	17	15	6	100.0	4.1	6.1	4.1	8.2	34.7	30.6	12.2
White female	36	0	1	1	5	9	13	7	100.0	0	2.8	2.8	13.9	25.0	36.1	19.4
Negro male	32	1	1	3	5	10	8	4	100.0	3.1	3.1	9.4	15.6	31.2	25.0	12.5
Negro female	29	0	2	1	7	4	12	3	100.0	0	6.9	3.4	24.1	13.8	41.4	10.3
Femur, total	146	0	0	1	12	59	61	13	100.0	0	0	0.7	8.2	40.4	41.8	8.9
White male	49	0	0	0	6	18	19	6	100.0	0	0	0	12.2	36.7	38.8	12.2
White female	36	0	0	0	1	12	20	3	100.0	0	0	0	2.8	33.3	55.6	8.3
Negro male	32	0	0	1	3	14	12	2	100.0	0	0	3.1	9.4	43.8	37.5	6.2
Negro female	29	0	0	0	2	15	10	2	100.0	0	0	0	6.9	51.7	34.5	6.9

Maturation at One Month

The foregoing discussion has considered chiefly the incidence of delayed maturation of centers of the proximal tibia and os calcis and the average dimension of the distal femur center as observed shortly after birth. Variation in size of the centers and the complete range of measurements for these

FIG. 5 FEMUR – SIZE AND PER CENT RETARDED MATURATION ACCORDING TO STUDY GROUPS

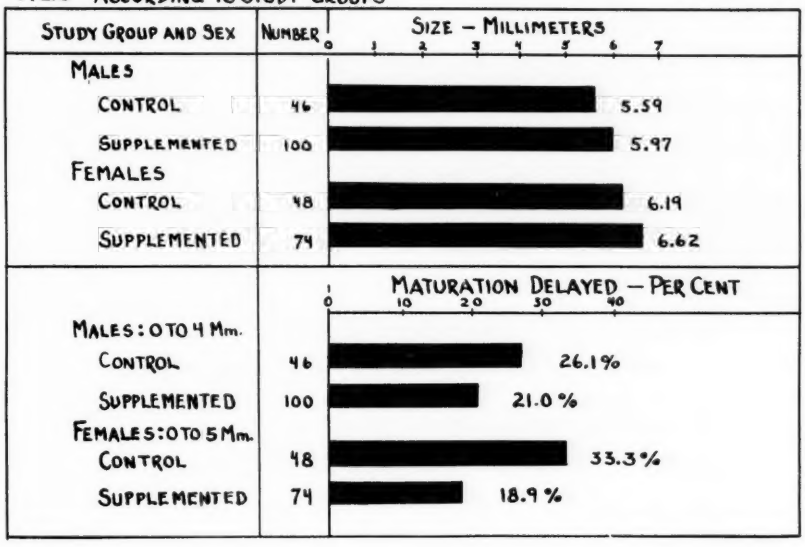
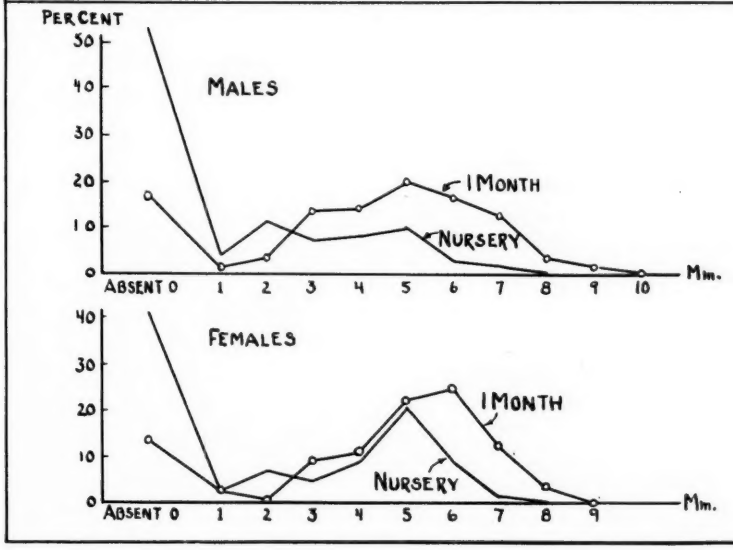
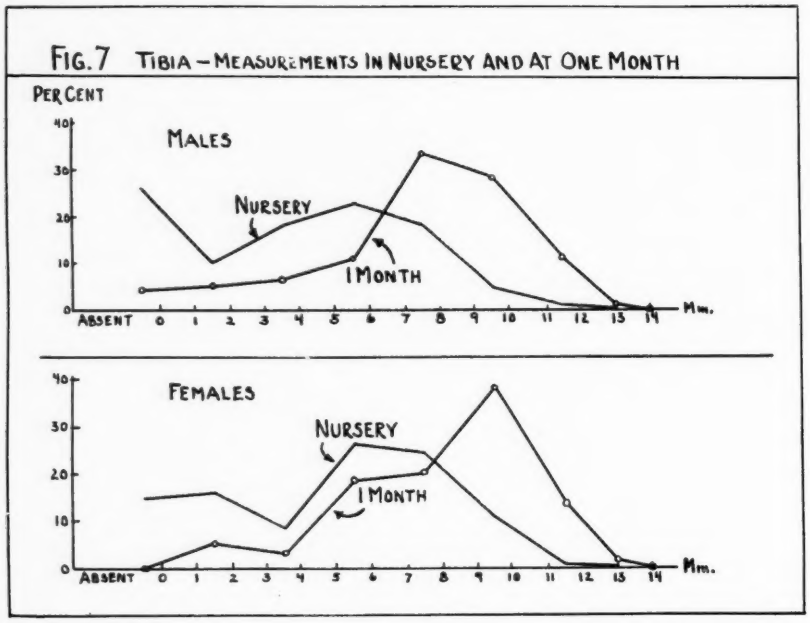


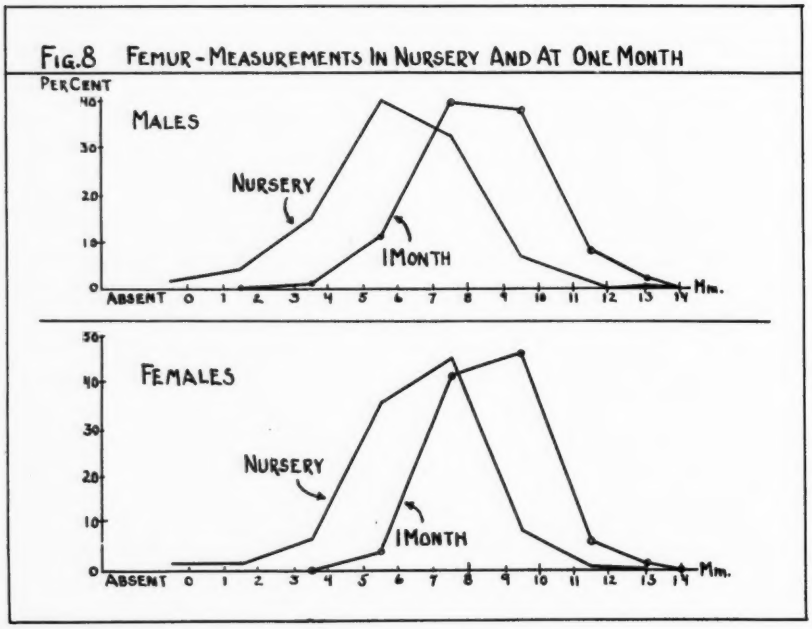
FIG. 6 OS CALCIS – MEASUREMENTS IN NURSERY AND AT ONE MONTH



infants at birth are shown in Figs. 6, 7, and 8 (Tables I and II) and compared with the measurements from x-rays taken at 28 to 36 days of age. X-rays at one month were available for approximately one-half of the babies.

Fig. 6 compares the measurements of the os calcis in male and female babies at birth and at one month. When present at birth, most of the centers measured 3 to 6 mm. in both males and females, and the maximum was 8 mm. At 1 month, the centers have increased very little; the majority are





4 to 7 mm. and there is only one baby with a center of 9 mm. Essential differences in the degree of maturation have not occurred. Among the babies in whom the os was absent at birth, approximately one-third still did not have a developed os calcis at one month.

Sex and race differences were much less at one month, although the degree of maturation in females is slightly ahead of that of the male babies.

Fig. 7 indicates the percentage distributions of the transverse measurements of the epiphyseal center of the proximal end of the tibia at birth and at one month. Here also it will be noted that definite differences in the range of values did not occur, and there is greater concentration at one month near the upper limits at 7 to 10 mm. It is apparent, for both male and female babies, that if this center was well developed at birth its progress during the first four weeks was less rapid than if the center was just beginning to develop. The difference in the degree of maturation between male and female babies at one month is not significant; and the white and Negro babies did not differ in development.

Table III indicates the increment in millimeters from birth to one month in relation to the size of the tibial center at birth. It is quite apparent from this table that when the epiphyseal center comes under the growth-stimulating factor the rate of development is relatively rapid. When the center is relatively large at birth, the growth increment at the end of four weeks is comparatively small. This suggests that the rate of growth may be quite rapid until a certain stage is reached at which point the rate of maturation markedly decreases.

TABLE III. INCREASE IN SIZE OF TIBIAL EPIPHYSEAL CENTER IN KNEE FROM BIRTH TO ONE MONTH

INITIAL SIZE	NO.	AVERAGE AT 4 WEEKS	AVERAGE SIZE INCREMENT
1-3 mm.	29	7.1	4.7
4-5 mm.	20	8.1	3.6
6-7 mm.	40	9.3	2.7
8+ mm. (av. 8.8)	20	11.1	2.3

Fig. 8 compares the size of the epiphyseal center of the femur in the knee at birth and at one month. It is evident that there is not a significant difference between the male and female babies. It is also apparent that an essential difference does not occur in the degree of maturation by the end of one month; the largest center at birth and at one month measured 13 mm. It is again obvious from these data that the greater the development of the center at birth the less rapid the rate of maturation during the first four weeks of life. The transverse diameter averaged 8.5 mm. at one month, an increase of only 2.3 mm.; and this increment resulted chiefly from the greater growth of the smaller centers present at birth.

Summary

These data indicate a great variation among infants in the maturation of epiphyseal centers at birth, as has been reported previously. The growth pattern from birth to one month for the three centers examined, namely, the os calcis, proximal tibia, and distal femur, is consistent and gives evidence of very rapid growth in the early formative stage which is followed by a marked slowing in the rate of growth. As a result of this changing rate in the maturation process, individual variation is less as the time after initial formation of the center increases. Thus, at one month, significant differences between

whites and Negroes and between males and females have almost been eliminated. At birth, the least difference by race and sex is found for the center at the distal end of the femur, which is the most advanced; and the greatest difference is found for the os calcis, which is the latest of these three to be present in most babies.

The time of formation of the center appears to be the important factor of individual difference. Negroes tend to develop the centers earlier than whites, and for each racial group the female is more precocious than the male. The more advanced development of females at birth suggests that this may be a factor in their greater ability to survive. This interpretation, however, is not supported by the Negro babies, who are most advanced but have a higher neonatal mortality. Therefore, maturity at birth as indicated by the degree of maturation is only one factor, and not necessarily a critical one, associated with the ability to survive.

Apparently the tibial epiphyseal center in the knee should be present in a mature infant delivered at term, but is in an early stage of development. This center, therefore, can be a more sensitive index of infant maturity than the os calcis or femur. This is particularly apparent in the comparison between the supplemented and nonsupplemented groups. Among patients who took supplements there was a significantly greater probability that the tibial epiphyseal center of the knee would be present at birth, especially for female babies. For the male babies this significance is borderline.

Skeletal growth and maturation are obviously under control of a fundamental biologic growth mechanism. These data give suggestive evidence that nutritional factors may affect the efficiency with which this mechanism functions, but, in this group, the supplements given did not alter to a marked degree the appearance of epiphyseal centers. This population, however, was not experiencing any serious nutritional deficiencies. In fact, the patients who did not receive supplements reported a diet in the last half of pregnancy which included, on the average, 76 Gm. of protein and 860 mg. of calcium.

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Discussion

DR. ERNEST W. PAGE, San Francisco, Calif.—The study just presented is but one facet of a broad program of clinical investigation into the relationship of nutrition to pregnancy which Dr. Tompkins and his group, the Nutrition Research Clinic, have undertaken in the past 20 years. Some of their recent statistical correlations are of considerable clinical significance. They have shown, for example, that premature labor occurs in 22 per cent of women who are underweight, and that this high figure may be reduced to 9 per cent with appropriate protein and vitamin supplements during pregnancy.

In the present study Dr. Tompkins would, I am sure, be the first to agree that there is no convincing relationship between the nutritional status of the mother and the development of the epiphyseal centers in the lower extremity of the fetus. Considering the complexity of factors influencing skeletal growth, this is not surprising. There appears

to be statistical significance in the case of the proximal tibial center, but this is limited to female infants. In all this type of work, one must bear in mind that a statistically significant correlation does not per se establish any causal relationship. My friend, Dr. Leon Chesley, tells me that there is a statistically significant correlation between the occurrence of eclampsia and membership in the Baptist Church!

Christie[1] found that the proximal tibial epiphysis is present in 86 per cent of white females and 79 per cent of white males that weigh between 3,000 and 3,500 grams at birth; whereas in babies weighing from 2,500 to 3,000 grams the figures become 75 and 35 per cent, respectively. These data resemble those presented by Dr. Tompkins. Fetal size and sex play such predominant roles with respect to epiphyseal development that the possible influences of maternal nutrition may be obscured in relatively small groups of infants not identical in size and weight.

Much has been learned, of course, about the influence of various factors upon the rates of skeletal growth in animals, and most of these facts should be applicable to the human being. The primary factors which determine the time curve for skeletal development are species or genetic influences and chronologic age. Retardation of the growth and development of epiphyses, however, has been demonstrated with specific single deficiencies of vitamins A, C, D, folic acid, riboflavin, pantothenic acid, and pyridoxine. Each of these deficiencies, incidentally, is also capable of producing fetal anomalies. Retardation also occurs with the administration of estrogens or adrenocortical hormones; and, as shown by Francis, it is caused by any constitutional illness in infancy. On the other hand, acceleration of the first phase of skeletal growth results from the growth hormone, androgens, thyroid hormone (in the case of certain centers), and from diets high in casein, calcium, or fat.

To illustrate the complexities of the problem and the difficulties of interpretation, we are reminded that Wachstein and Gudaitis[2] conclude that all pregnant women on an average diet are deficient in pyridoxine (vitamin B_6), and that the minimal quantity needed in pregnancy to avoid an abnormal metabolism of tryptophane is 10 mg. daily. Pyridoxine, like other members of the B complex, is a cofactor for an essential enzyme system, such as transaminase. We are currently studying two groups of women, one given a supplement of 10 mg. of pyridoxine daily and the other receiving none. While we find it possible to elevate the transaminase content of the maternal blood cells when pyridoxine is added during the third trimester, we are unable to elevate the transaminase activity of the placenta. Possibly the fetal tissues receive all such cofactors in adequate quantities at the expense of the maternal organism unless an extreme deficiency exists. Thus the supplementation of an average maternal diet may not influence fetal growth perceptibly. Even if we could elevate the transaminase activity of the placenta, would it be—as a child so often asks—good or bad? By the same token, we might ask Dr. Tompkins, is an acceleration of epiphyseal development good or bad? Continued acceleration of skeletal maturation produces dwarfs, whereas it is delayed maturation that allows men, in general, to grow taller than women.

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THE PROBABILITY OF THE OCCURRENCE OF THE MORE COMMON TYPES OF GYNECOLOGIC MALIGNANCY*

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THE probabilities of the occurrence of cancer emphasize the importance of examining the patient. Mere knowledge of the probabilities may appear of little value to the clinician, for such information does not simplify the problem of evaluating the pelvic findings in every case. We believe, however, the data here presented will provide those interested in the relative frequencies of the different types of gynecologic malignancy with more reliable information than has been available in the past. Since our recommendations usually depend upon our opinion of the possibilities our patients face, agreement regarding the probabilities of malignancy appears desirable.

We also appreciate that, since surgery now so rarely involves a fatality or disabling complication, indicated minor operations are not infrequently discarded in favor of the more "definitive" measures advocated by Clark.[2] Perhaps the incidence of malignant disease in an organ does justify its removal as a cancer-preventing measure, but we believe we should be fully aware of the actual occurrence rates and the calculated probabilities that malignancy might develop in the tissues or organs under consideration.

Typical of the type of inaccuracies likely to be perpetuated in current discussion are the following:

> 1. We should realize that carcinoma of the cervix occurs three to five times more frequently than we can expect to find adenocarcinoma in the uterus. . . .

In the data to be presented it will be evident that while carcinoma of the cervix *is* four to five times more frequent than carcinoma of the corpus below the age of 40, cervical malignancy does not occur more often than corpus carcinoma after the age of 55 (Table I).

> 2. After the menopause, adenocarcinoma of the uterus should be considered first whenever vaginal bleeding occurs, for it is the most frequent type of pelvic malignancy to occur after the menopause. . . .

*Presented at the Seventy-seventh Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 20, 21, and 22, 1954.

While this is generally believed, the data showing the probability of an individual developing a malignancy indicates that except in the early seventies the *individual* is more likely to develop a carcinoma of the cervix than a malignancy in the fundus of the uterus (Table II).

> 3. Hysterectomy should rarely be considered as a prophylactic procedure, for not more than 1 per cent of women will develop a malignancy of the uterus. . . .

Actually from the data to be presented it will be evident that at some time during their life's span nearly 4 per cent of women (after the age of 20, 2.28 cervix plus, 1.55 corpus) are now developing a malignancy of the uterus.

We believe that the most accurate available data regarding the incidence of the various types of malignancy in our population are, at the present time, those from the Health Departments of Connecticut and New York. Cancer has been a reportable disease in both states for many years. In New York, with hospitals, pathologists, and physicians reporting since 1940, the records of the Bureau of Cancer Control indicate the magnitude as well as the direction of the cancer problem. From this State (exclusive of New York City), figures on cancer incidence, mortality, and expectancy were first reported by Levin and Goldstein[10] in 1947 at the Fourth International Cancer Research Congress.

We are likely to think of the probabilities of the occurrence of cancer in terms of our own chance of developing malignancy. Present data indicate that, at least in Connecticut and New York, approximately one of each 4 individuals under 40 years of age will eventually develop some type of malignant neoplasm. While this eventuality is impressive, we should, as physicians, be more interested in the probabilities of the occurrence of cancer in terms of the patients we examine each day.

It does not seem particularly helpful for the physician to know that some one of each four of his patients will eventually develop some type of malignant disease. Such knowledge of the probabilities would be of interest to the legendary family doctor who knew and watched his patients from their cradle to his grave. Few of us now, however, expect to be able to keep an eye on any appreciable number of our patients for more than a few of the years of their lives. We should, therefore, as gynecologists, be most interested in learning the number among the women we examine who might be developing a gynecologic malignancy at the age when they are examined.

New York's most recent figures on the incidence of the more common types of gynecologic cancer are illustrated graphically in Fig. 1.

Taking figures from the statistician's graph, we find data which may be expressed in terms of the proportion of women in each age group in whom cancer might be expected to occur during any one year. If we are to do annual pelvic examinations, it thus appears that the probability of detecting malignancy of the specific types or sites indicated would, in each age group, approximate the figures shown in Table I.

Considering these data (Table I) we might well question the economic feasibility of cancer detection clinics—particularly if the patients accepted for such gynecologic examination are restricted to those without symptoms or

TABLE I. ANNUAL AVERAGE CANCER INCIDENCE* RATES,† FEMALES BY AGE AND SITE, NEW YORK STATE, EXCLUSIVE OF NEW YORK CITY, 1949-1951

SITE	AGE IN YEARS													
	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Breast	1.05	5.34	15.47	38.36	77.30	96.80	108.44	135.33	161.16	188.45	245.48	274.54	307.68	337.52
Cervix uteri	2.23	8.54	21.16	36.24	50.32	56.60	56.56	58.78	57.93	62.90	50.52	56.68	48.23	58.63
Corpus uteri‡	.39	1.30	1.33	5.75	11.6	28.0	41.56	56.49	57.93	57.18	54.93	52.25	44.37	38.03
Ovary	1.18	2.13	3.14	7.00	13.22	18.37	27.66	31.33	33.10	37.04	43.06	32.53	24.11	28.52
Vulva	—	.47	.12	.50	1.48	1.66	2.03	1.94	3.72	9.45	13.56	14.29	19.29	15.85

*Includes cases reported only by death certificate.
†Rates are per 100,000 females per 1950 census.
‡Excludes "uterus unspecified."

signs of pelvic malignancy. The New York data clearly indicate that during any one year we should not expect to find more than one malignancy of the cervix per 10,000 women examined in their twenties (if they have no predisposing pathology or symptoms), nor more than 6 cases per year per 10,000 women over 40 years of age. It is equally interesting to note that no more than 3 women per 10,000 in their 40's will develop an adenocarcinoma of the uterus in any one year, and that the annual occurrence rate of corpus cancer

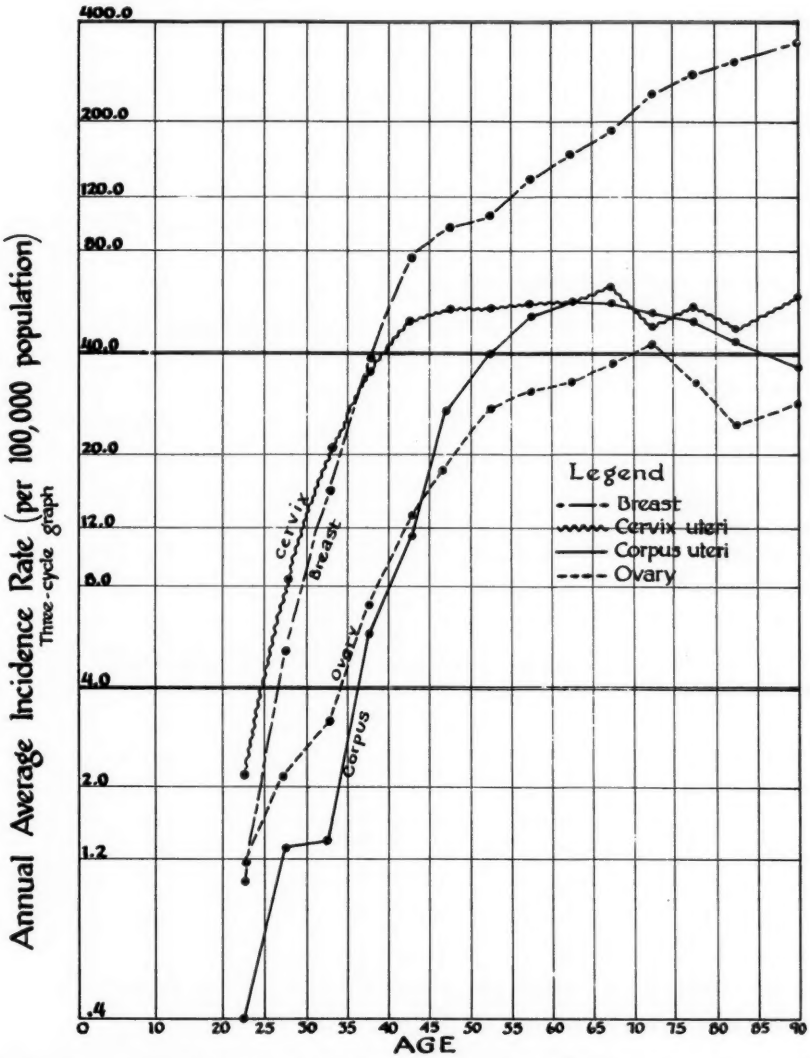

Fig. 1.—Annual average cancer incidence rates among females, for gynecological sites, by age, New York State (exclusive of New York City) 1949-1951.

Note.—There were 2 cases of breast cancer, 4 of ovarian cancer and 2 of uterine cancer under age 20 in 1949-1951. The rates for the age group 85 and over are plotted at age 90.

parallels the frequency of cervical malignancy after the woman's fifty-fifth year. As practical figures to remember, we might emphasize that the incidence of previously unrecognized cervical malignancy begins to exceed 4 new

cases per 10,000 adult women per year when those being examined are more than 39 years of age, while the annual occurrence rate of corpus cancer does not exceed 4 cases per 10,000 except among women more than 53 years of age.

These data are based upon the reported occurrence of cases in an area where the population is known and where, for the most part, medical facilities are adequate and women are examined fairly often and where, with increasing frequency, cases of malignancy are being detected in an early stage.[15] During the years 1949-1951, among the two and one-half million adult women (according to the 1950 census, 2,465,309 over 20 years of age) in Upstate New York, new cases of gynecologic cancer reported per year averaged as follows: breast 2,191; cervix 969, fundus 595; and ovary 414. This indicates an annual occurrence rate of one new case of cervical carcinoma per year among each 2,544 women over 20 years of age. During the years surveyed we believe there was an insignificant number of Stage 0, cervical carcinomas in situ, and to date there is no evidence to indicate an increase of in situ diagnosis in the cervical lesions reported. We were surprised to learn that the occurrence rate of cervical carcinoma decreased slightly during 1948-1952, while the rate of fundus lesions increased slightly during the same five-year period.

The probabilities of cancer occurrence, as indicated in the annual incidence rates for the State of New York (exclusive of New York City), are lower than many current data would lead us to expect. We often hear that gynecologists see women with a much higher incidence of pelvic carcinoma than could be detected among that larger proportion of the population who have no reason to suspect that they might be developing a neoplasm. The thoroughness of the physician's effort to detect malignancy obviously determines his ability to pick up lesions at a very early stage of their development. In the cancer detection clinics, where supposedly only healthy women are being examined, the incidence of gynecologic malignancy is certainly several times higher than the annual occurrence rates in New York would lead us to expect. At the Cancer Detection Center of the Meyer Memorial Hospital[13] (Erie County Hospital, Buffalo, New York) for instance, in the years 1949 and 1950, among 941 women examined (205 under 35 years of age), 3 carcinomas of the cervix were found, an incidence of one case per 314 gynecologic examinations. Again, during the years 1952 and 1953, among 1,063 women examined in the same Center (231 under 35 years of age), 5 carcinomas of the cervix and one corpus carcinoma were found, an incidence of one uterine malignancy per each 177 women examined.

The following quotation from the Medical Director's recent report[4] is of interest:

> In five and one-half years of operation . . . we have examined approximately 5000 women over 30 years of age . . . and have picked up 17 carcinomas of the cervix . . . nine classified by the pathologist as carcinoma-in-situ and eight as early or Stage I lesions. In the same years, five adenocarcinomas of the uterus were detected . . . four had some complaint of bleeding while one had only a tumor detected on examination . . .

We believe, therefore, that the occurrence rates for the State of New York probably do not indicate how many unsuspected malignancies can be detected

among women without symptoms. The higher discovery rate by detection procedures among symptomless women, than by routine medical practice among women with symptoms, may be due to a relatively long time period on the average between the actual development of cancer and the onset of symptoms. This would suggest that there is at any given time a large number of women with symptomless cancers, only a small proportion of whom enter the symptom (usually detected clinically) stage in any given year.

In addition, an unknown proportion of symptomless and in situ stage cancers may never proceed to the symptom stage and may thus never get into the State's reported "incidence" figures.

Thus it is evident that in the Detection Centers, as well as in the hands of the more capable and thorough clinicians, a higher than the New York "expected" incidence of malignancy may be recognized due to the detection of cancer in an asymptomatic or preclinical stage.

The gynecologist probably will find his personal impression of the frequency of carcinoma in the woman's pelvis reflected, not in the annual incidence rates just discussed, but in the New York tables showing the calculated probability *of the individual's* developing one of the more common types of gynecologic malignancy. Such estimated probability rates for selected female sites were calculated[8] for the years 1949-1951 and published[20] on the basis of the 1950 U. S. Census figures. Table II illustrates the calculated probability of "risk" to any woman of developing one of the more common types of gynecologic cancer after the ages stated.

TABLE II. PROBABILITY OF DEVELOPING CANCER FROM INDICATED AGE ON, FOR SELECTED SITES BASED ON CANCER MORBIDITY REPORTS, NEW YORK STATE, EXCLUSIVE OF NEW YORK CITY, 1949-1951

(Probability Expressed in Per Cent)

	Probability of Developing Cancer After Indicated Age per 100 Women					
AGE	ALL SITES	BREAST	CERVIX	CORPUS UTERI	OVARY	VULVA
0	23.266	5.181	2.211	1.505	0.938	0.182
5	23.759	5.307	2.265	1.542	0.961	0.187
10	23.767	5.320	2.270	1.545	0.963	0.187
15	23.774	5.329	2.275	1.548	0.965	0.188
20	23.777	5.346	2.282	1.552	0.965	0.188
25	23.765	5.364	2.281	1.553	0.964	0.189
30	23.701	5.369	2.252	1.554	0.959	0.188
35	23.534	5.340	2.163	1.557	0.952	0.189
40	23.167	5.222	2.009	1.549	0.930	0.189
45	22.481	4.948	1.794	1.524	0.884	0.186
50	21.534	4.621	1.557	1.426	0.820	0.183
55	20.280	4.287	1.332	1.275	0.718	0.182
60	18.744	3.887	1.104	1.054	0.606	0.185
65	16.931	3.469	0.900	0.842	0.498	0.185
70	14.923	3.035	0.689	0.654	0.382	0.166
75	12.571	2.512	0.555	0.481	0.247	0.136
80	10.294	2.010	0.402	0.323	0.163	0.113
85	8.620	1.700	0.359	0.231	0.144	0.080

Table II indicates that, during their lifetime, approximately 10 among each 100 women will develop some form of gynecologic malignancy (after the age of 30, 5.3 women per 100 will develop a carcinoma of the breast and 4.8

a malignancy of the cervix, fundus, or ovary). This type of data will not be as helpful to the clinician, however, as would be a demonstration of the means of identifying those individuals predisposed to the development of malignancy before establishment and the beginning extension of the growth. While little progress has been made toward recognition of general or systemic "susceptibility," there has been considerable discussion of factors which seem to predispose the individual to the development of malignancy of certain types or of specific sites.

The possibility of preventing the development of a particular malignancy in an evidently predisposed individual, by eradication of a "precancerous" type of lesion has received considerable attention in the literature. It is obviously difficult to evaluate procedures employed in an attempt to eliminate individual susceptibility. While such predisposition can be suspected, it appears to be most difficult to demonstrate. We should be mindful, however, of the apparent effectiveness of measures which seem to have reduced the incidence of a particular malignancy within a group of supposedly predisposed individuals. In an effort to prevent the development of cervical carcinoma, for instance, Pemberton,[18] Cashman,[1] and Hepp[7] have reported on the apparent effectiveness of cleaning up the lacerated, eroded cervix by repair or deep cauterization procedures. The incidence of malignancy among women so managed, perhaps after they have been followed over a longer period of time than has been reported to date, seems to be necessary before final evaluation of the prophylactic value of the procedures recommended.

The necessity of a virtually lifetime follow-up is just as evident when we consider published data regarding factors apparently predisposing the individual woman to the development of an adenocarcinoma of the uterus. The incidence of adenocarcinoma has been reported to be three to four times greater in women who had experienced excessive dysfunctional bleeding at the menopause.[3, 19] At one time, there seems to have been a rather general feeling in the United States that the risk of endometrial cancer in later years might be considerably reduced by the relatively simple expedient of castrating, by irradiation, women who bleed excessively during their preclimacteric years. In all probability, however, this management was employed by many physicians who did not necessarily believe that factors responsible for the woman's menorrhagia at the menopause might be predisposing her to adenocarcinoma.

Evaluation of the endocrine background which some have believed predisposes the "preclimacteric bleeder" to adenocarcinoma should probably not be undertaken without also taking into account the irradiation therapy often employed in the management of menorrhagia at the menopause. Reporting the occurrence of carcinoma in the pelvis during a long period of follow-up (all cases followed more than 12 years; average follow-up 16.08 years), Palmer and Spratt[16] recently noted that approximately six times as many cases of corpus cancer had developed among 721 women whose preclimacteric bleeding had been stopped by irradiation as the data in Fig. 1 would lead us to ex-

pect in such a group, if they were *not predisposed* to adenocarcinoma of the uterus. Such data might be considered only as additional evidence that women with benign causes of excessive bleeding before the menopause have a greater than average chance of ultimately developing adenocarcinoma of the uterus. Scheffey[21] in 1942 expressed doubt that the use of irradiation for "benign bleeding" affected the eventual development of carcinoma in the same uterus. Palmer and Spratt emphasize, however, that the irradiation employed for castration might be an important factor in the noticeably increased occurrence of carcinoma in the areas irradiated, particularly since an increased incidence was evident not only in the cervix and fundus but throughout the area irradiated, i.e., in the bladder, vagina, rectum, and vulva as well. Consideration of the possibly carcinogenic effect of such qualities and quantities of irradiation is not within the scope of this discussion. In view of such recent reports, however, we are unable to conclude that irradiation sufficient to assure castration can be expected to decrease the ultimate incidence of fundas cancer among women so managed, even though such irradiation effectively controlled the menorrhagia before the climacteric.

Any concept of "predisposition" or an individual susceptibility to malignancy assumes that the individual who develops malignancy possesses a constitutional factor that we cannot identify at the present time. Evidence that a degree of constitutional predisposition to develop malignancy may persist in the individual in spite of successful treatment of an initial carcinoma should perhaps receive more consideration. The effectiveness of present methods of treatment employed in an ever-increasing percentage of clinically early cases of cervical and fundal malignancy will probably soon turn the gynecologist's attention to the problem of "multiple malignancies." What does successful treatment of one primary carcinoma, resulting in long-time clinical cure or arrest of the disease, do to an individual's chance of ultimately developing another primary carcinoma in an entirely unrelated site? Warren, Lombard, and Levin,[11, 22] and others have suggested that the high frequency of cases of multiple malignant growths may be attributed to susceptibility or predisposition to cancer in some persons or groups of persons.

If a group of individuals survive the treatment of a first carcinoma for a number of years, and develop fewer second malignancies than might be anticipated (in accordance with published data regarding the probability of a second primary), it appears reasonable to assume that the measures employed to control the first growth had, in effect, created a decreased susceptibility to the development of other malignant growths. In this regard it seems timely to attempt to determine if the individual whose carcinoma is detected early becomes "cancer resistant" to a greater degree when the clinical cure is effected by irradiation or by surgery. Healy[6] has reported an incidence of 2.25 per cent second primaries among women with cervical cancer "cured" by irradiation, a figure strikingly paralleled by the results observed in a series of radiation-treated malignancies in the nasopharynx and larynx. M. Lederman[9] observed only 25 second primaries among 955 such malignancies treated by irradiation alone, an incidence of 2.62 per cent.

In a more recent follow-up study Palmer[17] has noted a total of 23 instances (excluding skin cancers) of a second primary developing among 469 women who survived the irradiation treatment of a carcinoma of the cervix with "no evidence of disease" for more than 15 years. Palmer's 5 per cent incidence of second malignancies among long-time irradiation cures is more in agreement with Warren's[23] statement (based on careful study of autopsied cases) that 6 per cent of patients can be expected to develop "multiple primaries."

Many of the data available regarding "multiple primaries" are, however, rather difficult to evaluate. In a number of the cases reported one of the "multiple malignancies" was a skin cancer, a lesion which should probably be considered as a separate problem. We might well keep in mind, however, the possibility that in those individuals who achieve long-time "cure" by irradiation, a degree of immunity to the development of a second malignancy may be realized which is not evident among women whose initial carcinoma was treated and apparently "cured" by surgical excision of the growth.

Thoughtfully collected data will be necessary if a significant and reliable study is to be reported.[14] The incidence of second primaries in a group of individuals whose first malignancy was of a type usually treated by irradiation, compared to the incidence of a second primary among patients who survive the surgical excision of a lesion not ordinarily treated by irradiation, would not help answer the question. We should take into consideration, for instance, that carcinomas of the breast are not unlikely to occur bilaterally and that malignancies of the large bowel, over a period of years, are often multiple. Since malignancies of both the bowel and the breast are usually treated by surgical resection, a study of the incidence of second primaries among such groups of cases would be very likely to make surgery appear ineffective as far as the prevention of a second malignancy is concerned.

In view of the predictions of Meigs[12] and the work by the Grahams,[5] indicating a cytoplasmic change in the nonmalignant cells of individuals who have a "good result" after irradiation, a change that is not observed in the cells of individuals who do not have such a good response, a more reliable method of recognizing the patient who will have a good result by irradiation appears imminent. It seems timely also to look for more evidence that irradiation creates, in some cases, a "resistance to malignancy" that may not be appreciable in the follow-up of patients treated by surgery for the cure of their first malignancy.

Finally, if we are at times inclined to feel that the importance of malignancy is being overemphasized, a review of our own experience will usually indicate the desirability of continued efforts to solve the problems of malignancy. In the Buffalo General Hospital, an institution typifying conditions requiring hospitalization in an urban area, only the causes of fetal death terminate more lives on the obstetric and gynecologic services than are accounted for by the malignancies with which we have to deal. Moreover, efforts made in recent years have succeeded in reducing our fetal losses as well as the number of maternal deaths. During the four years 1946-1949, for example, the

uncorrected over-all fetal loss (past the twenty-eighth week of gestation) averaged 34.75 per 1,000 births, whereas this figure had been reduced to 31.25 per 1,000 births during the years 1950-1953. ("Corrected" fetal mortality for 1950-1953 averaged 1.27 per 1,000.) Among patients admitted to the Hospital's obstetric beds during the years 1949-1953, obstetric deaths (maternal) averaged 2.8 per 10,000 births, whereas 61.5 deaths occurred per 10,000 women admitted to the gynecologic beds. On the gynecologic service, deaths due to causes other than malignancy occurred at the rate of 0.63 per 1,000 admissions during the years 1949-1953, but pelvic malignancies, accounting for 90.7 per cent of the gynecologic deaths, increased our fatalities from 0.63 to 6.15 per 1,000 gynecologic admissions during that time.

Summary

The probabilities of an individual developing some of the more common types of gynecologic malignancies have been reported. Calculated annual incidence rates in each decade of life, for each lesion, are based upon the reported occurrence of specific gynecologic malignancies among adult women in the State of New York (exclusive of New York City) during the years 1949-1951.

Obstetricians and gynecologists will be particularly interested in the relative frequency of the gynecologic malignancies reported after the age of 40. The probabilities appear as follows: breast 5.2 per cent, cervix 2.0 per cent, fundus uteri 1.5 per cent, ovary 0.9 per cent, and vulva 0.2 per cent.

Considerations of factors thought to affect the probability of an individual's developing specific types of malignancy are briefly reviewed. It is suggested that determination of the incidence of a second primary, after apparent cure of an initial malignancy, may be found to provide another measure of the relative effectiveness of irradiation and surgery. It appears advisable to evaluate irradiation techniques as compared to operative procedures in terms of the apparent ability of each to affect those factors which seem to account for an individual's predisposition to develop multiple malignancies.

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Discussion

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—Dr. Randall has rendered us a distinct service by presenting statistical and factual evidence of notable importance with respect to the probability of occurrence of malignancy in its various sites and among progressive age groups. In this regard he expresses a wise philosophy when he states that, because of present-day technical advantages, we are likely frequently to consider major gynecologic procedures from the viewpoint of prophylaxis instead of relying upon an indicated minor approach to the immediate problem at hand.

It is fortunate that reliable data upon which to base the essayist's remarks are being accumulated in the states of New York and Connecticut, which tend to show that one of 4 individuals under 40 years of age will eventually develop some type of malignant lesion. From this base line Dr. Randall eventually points up for us the probabilities which we as gynecologists can expect among the women who consult us, either because of symptoms or for a routine health examination, together with the probable incidence of pelvic malignancy in the sites likely to be seen in the supposedly well women examined in cancer detection clinics and in relation to their age groups as well.

I shall not rehearse the data that have been presented except to emphasize that the expectancy is one cancer of the cervix per 10,000 women during the twenties, and not more than 6 per 10,000 after 40; and that after 57, cervical malignancy parallels the annual incidence of corpus cancer. Also, that no more than 3 women per 10,000 in the forties should develop corpus cancer. He states, however, that previously unrecognized cervical cancer begins to exceed 4 cases per 10,000 per year until after 39, and that the occurrence rate of corpus cancer does not exceed 4 cases per 10,000 until after the age of 52. The number of stage O carcinoma in situ is insignificant, he states, as far as evidence of increased diagnoses is concerned.

In further studying the cancer incidence rates presented from New York State, he has told us that certain detection centers present surprisingly higher figures, as for instance an incidence at the Meyer Memorial Hospital Clinic of one case in 314 gynecologic examinations, or 0.31 per cent.

At the detection centers in Philadelphia from 1944 to 1953, 27,355 were examined, of whom approximately 80 per cent had "repeat" examinations, amounting to one or more; 61 cancers were detected, the incidence of gynecologic cancer, including breast, being:

Cancer of cervix	14	0.051 per cent
Cancer of corpus	10	0.036 per cent
Cancer of ovary	4	0.014 per cent
Cancer of vulva	0	0.000 per cent
Cancer of breast	33	0.120 per cent

Since the data from New York State are based upon single examinations only, these data are not comparable.

In contrast with the previously mentioned annual incident rates, we are startled to learn from Table II that, according to the probability rates based on cancer morbidity rates studied by Dr. Randall, 10 women among each 100 will likely develop some form of pelvic and breast malignancy, i.e., after the age of 30, 5.3 are doomed to have cancer of the breast

and 4.8 malignancy of cervix, corpus, or ovary, a progressively increasing peak from younger decades, and with a gradually declining but "leveling" incidence thereafter compensated for, one would think by deaths due to systemic disease of advancing years.

That the statistical data reviewed are likely to cause us to revise some of our categorical teaching statements with regard to probable development of malignancies is evident from Dr. Randall's pertinent quotations of such instances.

"Systemic susceptibility" to malignancy remains an unknown factor, as Dr. Randall says, but I feel strongly, as I am sure most others do, that from the clinical standpoint the correction of the abnormal cervix with adequate histologic study of necessarily inclusive tissue (i.e., circular cervical biopsy with electrodessication and accompanying fractional curettage) is the best procedure that we can follow to attain two objects with one procedure: diagnosis of cancer on the one hand and restoration of the cervix to a healthy state, a method that we have advocated and pursued on our service at Jefferson Medical College for the past decade, observing the follow-up with satisfaction and with the belief that it is even more desirable than the simple cauterization of the cervix as carried out in earlier days. It is true, of course, that consistent follow-up of such a seemingly prophylactic measure envisages an effort beyond the lifetime of the observer and even that of his successors, as Dr. Randall says; in the meantime we should follow what we believe is good preventive medicine.

I am glad that the question of the carcinogenic effect of the use of irradiation principally with radium for the treatment of benign bleeding enters into the discussion. My own interest in this dates back a decade or more, as indicated by Dr. Randall in his paper, when I presented material before this Society that indicated, by a meticulous study of 7 patients who subsequently developed cervical carcinoma, 12 who developed corpus cancer, and one who developed corpus cancer and one corpus sarcoma, that "errors of omission, either in technique or in judgment . . . and not the irradiation therapy itself were the responsible factors in the subsequent occurrence of malignancy. . . . There was no factual evidence that irradiation had either retarded or accelerated the development of the cancer, such a sequence being purely speculative."

It is unfortunate that the very fine paper of Corscaden, Fertig, and Gusberg has been misquoted and misinterpreted so widely, for the idea is prevalent that their findings indicated that the use of radium for the control of so-called "benign" uterine bleeding has a positive carcinogenic effect. This is not in accord with the printed text, which reads: "It is inferred that the endometria of uteri which bleed abnormally prior to the menopause are predisposed to the subsequent development of carcinoma of the corpus." In other words, the importance of the contribution was to call attention to the fact that a greater proportion of corpus cancer is statistically likely to appear in those who have abnormal uterine bleeding prior to or at the menopause. Studying this problem from the opposite angle, recent reports by J. M. Hundley, J. B. Montgomery, R. M. Hunter, and their associates, analyzing the follow-up of large groups of patients treated with radium for benign uterine bleeding, show that, with proper criteria for its use, there was no more than the usual incidence of uterine cancer observed and in the order of the probability figures that Dr. Randall has presented. It is the abuse, not the proper use, of intracavitary radium that is at fault, and one must bear this in mind when evaluating the history of the patient with premenopausal and menopausal bleeding abnormalities. Palmer, quoted by the essayist also, states his belief that castrating dosage does not decrease the ultimate incidence of corpus cancer when employed to control "benign" bleeding, concluding as do Randall and others that this is additional evidence (721 patients followed for more than sixteen years; six times as many corpus cancers developed in the incidence and probability figures shown us) that it is the factors that promote excessive premenopausal and menopausal bleeding which also predisposes to the later development of corpus cancer, in which persistent and bizarre hyperplasia plays a part, that must be evaluated thoughtfully for definitive management. Palmer goes a step further, however, and suggests the provocative thesis that castration irradiation per se might affect local and adjacent sites as a carcinogenic agent in accounting for the noticeably increased evidence of cancer in such areas.

The essayist raises the question as to what influence successful arrest of a primary malignancy, either by irradiation or surgery, may have with regard to the acceleration or retardation of primary cancers elsewhere. His speculation as to the influence that radiosensitivity or resistance exerts, as contrasted with definitive surgery, and how these factors influence individual susceptibility toward second primary cancer is pertinent indeed, as are his thoughts regarding possible avenues of solution. That deaths due to gynecologic cancer represent over 90 per cent of gynecologic mortality on his hospital service is mute evidence of the gravity of the problem.

Of practical value to us, then, are the values given us that should aid in making decisions as to the diagnosis and treatment of those patients with or without symptoms who come to us for advice and reassurance as to possible or probable malignancy. To what has been said by Dr. Randall, I would add the following clinical probabilities for purposes for re-emphasis:

1. Nearly 30 per cent of the cervical cancer seen in the Jefferson Clinic over a period of 30 years has occurred in women 40 years of age or younger; 3 per cent are under 30.
2. Suspect endometrial cancer between 40 and 50 in every woman with fibromyomas and when metromenorrhagia is present.
3. Remember the syndrome of obesity, hypertension, diabetes, and a normal blood count, a common pattern of women 50 and over with endometrial cancer.
4. Beware of the obese patient, irrespective of age, with slightly abnormal bleeding or none at all, in whom ordinary pelvic examination is inconclusive, either with regard to palpation of the uterine fundus and/or the adnexa, for an ovarian or tubal malignancy is a primary probability.

DR. E. STEWART TAYLOR, Denver, Colo.—I have done some quick arithmetic as I sat listening to this paper and roughly estimate that if there are 125,000,000 people in this country of whom 30,000,000 are women over 40; and if you take 5 per cent of that 30,000,000 there will be 1.5 million who develop uterine carcinoma. But there are only 17,000 women who die annually in this country from carcinoma of the uterus. There is a big difference between Dr. Randall's 1.5 million individuals who will get carcinoma of the uterus and those that die each year. The death rate of 17,000 is the figure reported by the United States Public Health Service. Perhaps the answer to my question is obvious, but I should like to hear from Dr. Randall concerning my rapid arithmetic, and the apparent difference between the annual death rate and the 1.5 million who may be expected to develop cancer after age 40.

DR. RANDALL (Closing).—If you are to remember any of these figures, remember that there is a great difference in "*probability,*" which refers to the chance of the individual developing carcinoma during her lifetime, and the "*incidence*" or occurrence rate, which refers to the number of cases of carcinoma which might be found in any group of women in any one year. It is not correct to say that the probability of developing carcinoma of the uterus is 2 per cent, of fundus carcinoma 1.5 per cent, and that the probability of ovarian carcinoma is 0.9 per cent, and add it up to 4.6 per cent gynecologic carcinoma among any 100 women at any one time. The "*probability*" figures refer to what will happen among any 100 women during their lifetime. To calculate the women over 40 who have carcinoma of the cervix at the present time, we have to figure it on the basis of an occurrence rate of 5 cases per 10,000 women per year. When we talk about 30 million women in the country over 40 at the present time, the probability of their developing a gynecologic malignancy during their lifetime should be calculated on the basis that 4.6 per cent of the 30 million women will eventually develop it, but at any one time only 5 out of each 10,000 would be found to have a carcinoma of the cervix or fundus. Obviously, it makes a great deal of difference whether we are talking about the occurrence or incidence rates per year or the individual's "probability" during her lifetime. Finally, may I emphasize again that I had nothing whatsoever to do with the calculation of these rates. I merely reported the figures that the statisticians have given us, for I think we should become familiar with the data available.

FEMINIZING MESENCHYMOMAS OF THE OVARY*

Includes 107 Cases of Granulosa-, Granulosa-Theca-Cell, and Theca-Cell Tumors

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TWELVE years have passed since the founding of the Ovarian Tumor Registry by the American Gynecological Society. Relatively few reports have appeared from this agency because insufficient time has passed to acquire five-year survival rates to determine the prognosis of certain tumors of malignant or doubtful nature. At the present time approximately 1,000 ovarian tumors with their clinical histories and follow-up data are on file in the registry. By the year 1954, the first 500 cases have completed a five-year survival period. Among these tumors 107, or 21.4 per cent, were in the group designated as feminizing mesenchymomas of the ovary.

Realizing the difficulties in interpretation of this type of submitted material, we will concentrate on three main objectives. First, the histopathologic diagnostic difficulties will be presented. Since honest differences of opinion existed among the expert gynecologic pathologists composing the committee (Drs. Robert Meyer, George H. Gardner, Karl H. Martzloff, Herbert E. Traut, Robert Faulkner, and Dr. Emil Novak, Chairman) an attempt will be made to portray these differences, and the method used in arriving at a final diagnosis and classification of the 107 tumors reported in this study. Second, the clinical features of feminizing mesenchymomas will be considered only when there are extreme differences from already accepted information. Third, the most important features of the study are the mortality rates and prognosis in the patient with feminizing mesenchymoma. The prognostic value of the presence of extension of the tumor beyond the ovary at the time of operation and the use of histologic grading of the tumors will be discussed.

No effort will be made to review the vast literature on the subject of feminizing mesenchymomas. Comparisons to the literature will be made when deemed pertinent to the proper orientation of the reader or when extreme differences from accepted knowledge are encountered.

Nomenclature and Historical Orientation

Selye credits von Rokitansky in 1859 as the first to describe an ovarian tumor which, although he did not label it as a granulosa-cell tumor, apparently would be described in this category at the present time. Lawson Tait as early

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as 1883 considered cancer of the ovary as a reversion process to a fetal type of growth and described a solid tumor of the ovary with minute cavities lined by epithelium interpreted as immature Graafian follicles. Acconci in 1890 also described a bilateral papillary cystoma of the ovary in which he saw "neoplastic egg formations." It was von Kahlden in 1895 who gave the entity the name of "adenoma of the Graafian follicle," and Schröder in 1901 used the term "folliculoma," a tumor imitating the granulosa cells with folliculoid rosettes. It was not until 1914 that von Werdt published 6 cases under the title "Über die Granulosazell Tumoren des Ovariums," that the more common term of granulosa-cell tumor was applied.

The history of the thecoma or theca-cell type of mesenchymoma also began with von Rokitansky in 1859 with his early publication on fibroma of the corpus luteum and was followed by Boshagen's description in 1904 of the entity of a hypertrophic corpus fibrosum. Most early investigators interpreted this type of tumor as a part of the involution of the ovary rather than as true tumor formation. It was not until Löffler and Priesel in 1934 described a tumor under the name of "fibroma thecocellulare xanthomatodes ovarii" that this type of mesenchymoma was recognized as a distinct entity.

In 1910, Lecène described a special category of tumor known as folliculoma lipidique which was also described in 1932 by Moulonguet. Novak considers this type of tumor to be an example of a luteinized granulosa-cell tumor. Recently, Teilum has suggested that the "folliculome lipidique" be separated from the feminizing mesenchymoma group of tumors and included under the term androblastoma. Teilum wishes to have the adrenal rest tumors, luteomas, and so-called masculinovoblastomas, as well as the folliculoma lipidique, under one heading because of their morphological resemblance to testicular tumors. At the moment this debatable point cannot be solved, hence in this treatise we have included 3 cases of folliculoma lipidique. It was also decided not to include a few examples of gynandroblastomas in this series since these tumors are composed of elements of both granulosa cell-tumors and arrhenoblastomas.

Since these first descriptions of the various types of mesenchymomas, literally hundreds of papers, including individual cases and reviews, have appeared. No attempt will be made to analyze this massive literature which has been excellently performed by Selye, Novak, Dockerty, Meyer and many others. Dockerty estimates the number of granulosa-cell tumors reported as 600 accompanied by about 100 theca-cell tumors. Numerous synonyms have developed over the last 50 years and include the following:

1. Adenoma of the Graafian follicle
2. Folliculoma of the ovary
3. Granulosa-cell tumor
4. Basal-cell tumor of the ovary
5. Kahlden's tumor
6. Malignant folliculoma
7. Folliculoid carcinomas of the ovary
8. Granlosa-cell carcinoma
9. Theloma
10. Granulosa-theca-cell tumors
11. Fibroma thecocellulare xanthomatodes ovarii
12. Löffler-Priesel tumor
13. Theca-cell tumor
14. Thecoma
15. Malignant thecoma
16. Folliculoma lipidique
17. Luteoma
18. Luteinized granulosa-cell tumor
19. Lutein-cell tumor of the ovary

Histogenesis and Experimental Production of Mesenchymomas

The past history of mesenchymomas illustrated the relation of the Graafian follicle and future development of tumor. These views were also concerned with the histogenetic aspects of the origin and embryology of the granulosa cell and the ovarian stroma. Gillman in an extensive paper on the histogenesis of the ovary calls attention to the fact that granulosa cells and stroma cells have different origins. He concluded that the theca cell is a modified stromal cell of mesenchymal origin and the granulosa cells of the primordial follicle alone, of the various cellular elements, arise from the celomic epithelium. Gillman stated that it would be unlikely that a granulosa cell can evolve into a theca cell and vice versa as Fischel and others have suggested. Meyer believed that masses of granulosal tissue, unused in the formation of the primitive follicle, may remain as rests of "granulo-saballen" which he believed constituted the source of future granulosa-cell tumors. Fischel, Meyer, and Politzer claimed that the granulosa is formed by differentiation from the ovarian mesenchyme which in turn develops into either granulosa or theca-cells. This concept would be more flexible in explaining the variable mixtures of granulosa and theca cells in so many of the tumors of this group.

In an effort to clarify the origin of these tumors, efforts have been made to study the problem in animals. Baumann and Weyel, as early as 1935, reported the natural occurrence of granulosa-cell tumors in animals. Mulligan describes both thecomas and granulosa-cell tumors in dogs; however, none of the tumors have had malignant qualities. Harvey, Dawson, and Innes reported the occurrence of granulosa-cell tumor in a calf and recently Willis described a racing mare which developed abdominal enlargement and at autopsy had a huge ovarian cystic mass weighing 20 pounds composed of solid and cystic masses of granulosal epithelium closely resembling the human variety of granulosa-cell tumor.

The experimental production of ovarian tumors has been of some help in the etiology of mesenchymomas. Two procedures have been used which retain some ovarian tissue but also prevent estrogen from reaching the anterior lobe of the pituitary in adequate amounts. The first of these methods is to submit the ovary to a dose of x-ray sufficient to destroy the oocytes and follicles without injury to the remaining ovarian tissue. The second method depends upon excision of both ovaries and implantation of an ovary into the animal's spleen where its hormones pass immediately to the liver and are inactivated.

Furth and Furth in 1936 submitted mice to general irradiation with x-ray and were able to increase the incidence of ovarian tumors about 15 times over their controls. Several of the tumors were granulosa-cell tumors. Furth and Butterworth in 1936, and a year later Traut and Butterworth submitted additional data on irradiation-induced neoplastic disease of the ovaries of mice. These workers were led to believe that the tumors originated from remnants of disorganized follicles. Kaplan found that irradiated ovaries transplanted into irradiated and nonirradiated spayed mice gave rise to granulosa-cell tumors, luteomas, and related neoplasms. Nonirradiated ovarian grafts on irradiated

spayed animals yielded only one sarcoma that may not have originated in the ovarian tissue. Apparently, intact ovarian endocrine function inhibits the development of tumors in irradiated ovaries. Geist, Gaines, and Pollack, in 1939, described in great detail the sequence of the production of granulosa-cell tumors in mice. The changes took place as follows:

1. Initial change—first two days, degeneration of primary oocytes.
2. Theca interna not destroyed—begins proliferation in first weeks.
3. Theca becomes progressively luteinized.
4. Complete luteinization in sixth and seventh months.
5. Follicular atresia complete at seventh week.
6. Tubular adenomas derived from surface epithelium appeared after six months.

These investigators concluded that the biologically active luteinized tumors were derived from an undifferentiated parenchymal cell of the ovary and that the granulosa cells of the Graafian follicles played no role in the genesis of tumor.

As early as 1937, Strong, Gardner, and Hill had transplanted a spontaneous malignant carcinoma of the ovary which produced hyperfolliculoidism. In recent years, Li and Gardner, and Biskind and Biskind have transplanted ovaries into spleens of castrated rats. Not all of the transplants were successful, but when the transplanted tissue survived, a continuous formation of primordial follicles developed which were luteinized. Since the follicle could not rupture, the ovum died and luteinization of the mature follicle took place from the periphery inward. At 157 days neoplastic cells appeared in the corpora lutea, and at 300 days granulosa cells appeared in the luteoma.

Additional experiments have illustrated that tumors induced in castrated male mice have been predominantly granulosa-cell tumors while those in female mice were either mixed granulosa-cell tumors and luteomas or pure luteomas. Interestingly, the injection of gonadal hormones in mice bearing intrasplenic ovarian grafts prevented the development of ovarian tumors. Most investigators, such as Peckham and Greene, have not been successful in demonstrating that spleen induced tumors from transplanted ovaries in castrated animals to be fully autonomous. Silberberg, Silberberg, and Leidleir studied the effects of subcutaneous anterior hypophyseal transplants on ovariectomized mice with intrasplenic ovarian grafts. Growth and age changes occurred in the grafted ovaries; proliferation of follicles and lutein tissue was stimulated, and intrasplenic tumors developed in which more luteomas were produced than granulosa-cell tumors.

Recently McKay, Hertig, and Hickey have postulated that granulosa-cell tumors of the human ovary have their origin in atretic follicles which contain persistent granulosa cells. They based their contention on the similarity of the residual granulosa cells in human ovaries to the processes described above in the production of granulosa-cell tumors by ovarian implants into spleens in experimental animals. These authors also supported their claims with illustrations of a small granulosa-cell tumor of microscopic size arising in an atretic follicle,

and examples of granulosa-cell tumors producing structures resembling atretic follicles. McKay and associates also have introduced the concept that theca-cell tumors have their origin in cortical stromal hyperplasia, maintaining that the histological pattern of both tissues is identical, including the presence of hyaline plaques. They demonstrated transitional stages between cortical stromal hyperplasia and thecomas. Woll and co-workers showed that patients with thecoma in one ovary invariably had cortical stromal hyperplasia in the opposite ovary.

The question of induction of granulosa-cell tumors in women following roentgen-ray irradiation has been illustrated and discussed by Traut and Butterworth, and McKay and his co-workers. Speert, however, collected a group of cases of irradiated women and found a very low incidence of ovarian tumors in this group and only one case of granulosa-cell tumor. Some data have been collected from histochemical investigations, such as that of McKay and collaborators, that the cells of the theca interna are the cells which produce estrogenic steroids in tumors as well as in normal ovaries.

In spite of the extensive work which has been done on the histogenesis of mesenchymomas there is no final proof as to their origin. Until conclusive evidence is introduced, however, compromises must be made. For this reason we will attempt to be judicious in using not only the term mesenchymoma but also the previous accepted terms such as granulosa-cell and theca-cell tumors in the remaining text of the paper.

Present Study and Histopathologic Difficulties

The Ovarian Tumor Registry at the present time consists of pieces of tissue and slides from approximately 1,000 ovarian tumors which have clinical histories and yearly follow-up data. Only the first 500 cases, however, have matured to at least a five-year follow-up period by 1954. This study consists of 107 ovarian tumors in the feminizing mesenchymoma group which were submitted to the Ovarian Tumor Registry in the period from 1942 to 1948. The distribution of the benign and malignant tumors among the first 500 tumors is as shown in Table I.

TABLE I

	NO.	PER CENT
Benign tumors	152	30.4
Malignant tumors	348	69.6
Total	500	100.0
Solid malignant tumors	277	79.6
Cystic malignant tumors	71	20.4
Total	348	100.0

Therefore, the 107 mesenchymomas represent 21.4 per cent of the first 500 tumors submitted to the registry. In addition, of the 348 malignant tumors the mesenchymoma group comprise 30.7 per cent; and of the 277 solid malignant tumors, 38.6 per cent. These data have no application to the clinical incidence of the respective types of tumors in the female population. They do indicate, however, the type of neoplasm in which either the pathologist or clinician has need for consultation and the type of material being forwarded to the registry.

The slides and histories were catalogued and submitted to the five consulting gynecologic pathologists of the Ovarian Tumor Committee for their diagnoses. Some difficulties were encountered because of poorly prepared slides, but in many instances new slides were prepared. The gross descriptions of the tumors followed the classical patterns and the sizes of the tumors in 107 cases are given in Table II.

TABLE II

	GRANULOSA-CELL TUMORS	GRANULOSA-THECOMAS	THECOMAS	TOTAL
Less than 8 cm.	31	9	8	48
8 to 20 cm.	36	9	4	49
More than 20 cm.	4	1	1	6
	4	0	0	4
Total	75	19	13	107
Bilateral tumors	11 (15%)	1 (5%)	0	12
Largest tumor	30 cm. dia.	10 by 26 cm.	30 by 40 cm. (30 pounds)	

With the complete histories and the diagnoses of the five gynecologic pathologists available, we made a systematic review of the cases in which at least one of the five consultants made the diagnosis of a type of feminizing mesenchymoma. When three of the five experts agreed on the diagnosis, the case was accepted, provided our own interpretation was in agreement. With only one or two of five in agreement on a tumor, these slides were again reviewed with the Chairman, Dr. Novak. If in our opinion enough criteria of the feminizing mesenchymomas were present, the case was accepted. In 107 cases a general grouping was as shown in Table III.

TABLE III

TYPE OF TUMOR	CASES	PER CENT OF TOTAL CASES
Granulosa	75	70.0
Granulosa-thecoma	19	17.8
Theca-cell	13	12.2
Total	107	100.0

TABLE IV

TYPE OF MESENCHYMOMA	NO. OF CASES
1. Mixed	21
2. Diffuse	19
3. Granulosa-thecoma	19
4. Microfollicular	15
5. Thecoma	13
6. Cylindromatous	9
7. Gyriform	4
8. Folliculoma lipidique	3
9. Tubular	2
10. Angiomatous	1
11. Sarcomatous	1
Total	107

The problem of specific types of feminizing mesenchymomas is a difficult one, but with the use of traditional classifications as described by Novak or

Selye, with slight modifications, 11 types of feminizing mesenchymomas were found. The variability of the microscopic patterns and the frequent occurrence of mixed types made classification fraught with great differences of opinion. The various types in descending order were as shown in Table IV.

No great purpose is served in typing granulosa-cell tumors except as a portrayal of their variable patterns which unfailingly tend to complicate the histopathologic diagnosis. In an effort to apply statistical analysis to the diagnoses made by the five members of the Ovarian Tumor Registry the following method was applied. In all, 463 separate diagnoses by these experts were tabulated as to correct or incorrect diagnosis. Considerable leniency was allowed in individual terminology within the numerous variations of the feminizing mesenchymomas. If, however, the diagnosis was in complete disagreement, for example, "sarcoma," "hypernephroma," "arrhenoblastoma," or "adenocarcinoma," it was tabulated as an incorrect diagnosis. The accuracy of the pathologic diagnosis in 107 cases of feminizing mesenchymoma is illustrated in Table V.

TABLE V

HISTOLOGIC PATTERN	NO. CASES	NUMBER OF DIAGNOSES	CORRECT DIAGNOSIS	PER CENT	OTHER COMMON DIAGNOSES
Mixed types	21	96	65	68	Adenocarcinoma,
Diffuse	19	82	58	71	carcinoma, etc.
Microfollicular	15	63	58	92	Carcinoma
Cylindromatous	9	42	31	74	Adenocarcinoma
Gyriform	4	18	18	100	
Folliculoma lipidique	3	14	8	57	
Tubular	2	8	3	37	Adrenal rest
Sarcomatous	1	5	2	40	Hypernephroma
Angiomatous	1	4	1	25	Sarcoma
Total granulosa group	75	332	244	73	Hemangioma
Granulosa-thecomas	19	74	59	80	Fibroma, sarcoma
Thecomas	13	57	40	70	Fibroma, sarcoma
Total mesenchymomas	107	463	343	74	

The explanation for the number of diagnoses not always appearing in multiples of five was the death of Dr. Robert Meyer, following which there was a period with four men on the Ovarian Tumor Committee. Among 20 deaths in this series of cases there were 90 separate diagnoses made by the consulting pathologists, of which 54, or 60 per cent, were considered to be in general agreement. The most common error was to call the original tumor an adenocarcinoma or sarcoma. The death cases were gone over separately a second time by the chairman of the registry committee and the authors of this paper for final verification and classification.

Assuming that the authors of this paper and the chairman of the American Gynecological Society Ovarian Tumor Registry have been accurate and fair in considering the 107 cases in this series to be all examples of feminizing mesenchymomas, the percentage of correct diagnoses made by other members of the committee as compared to the chairman would be as shown in Table VI.

TABLE VI

PATHOLOGIST	PER CENT CORRECT DIAGNOSIS
Chairman and Authors	100
Consultant Pathologist No. 1	71
Consultant Pathologist No. 2	70
Consultant Pathologist No. 3	65
Consultant Pathologist No. 4	65
Consultant Pathologist No. 5	59
Group score	74

Debatable Tumors and Variants in This Study

It is to be expected that in a series of tumors sent in for consultation many bizarre types would be seen. The extreme variations in patterns is undoubtedly responsible for the differences of opinion regarding the nomenclature and classification of the cases submitted to the Ovarian Tumor Registry. In general, our rule has been to demand that major portions of the tumor have cells resembling granulosa cells and evidences of growth characteristics identical with those of granulosal tissue. Least difficulty was experienced with the microfolliculoid (Fig. 1, *A*) and gyriform types, especially when the granulosa cells tended to arrange themselves in small clusters or rosettes around a central lumen (Fig. 1, *B*).

As previously mentioned, there were many cases in this report in which only one or two of the five members of the committee agreed on the diagnosis of feminizing mesenchymoma. After deliberation and review with the Chairman, Dr. Novak, 5 cases were deleted from the study. Six cases, however, which were debatable and presented some interesting variants, were retained in the study. These 6 cases will be illustrated with photomicrographs (Figs. 2-5). The first of the debatable cases, O.T.R. 199, represents a type of luteinization of both thecal and granulosal elements and in this case was confused with a Brenner tumor (Fig. 2, *A*). The second debatable tumor, O.T.R. 13 (Fig. 2, *B*), is an example of extreme luteinization of a granulosa-cell tumor which might fall into the category of the lipoid-containing tumors called "folliculoma lipidique." These tumors are usually of the tubular or adenomatous pattern, the tubules being lined by a single layer of clear-looking cells of short columnar type which are rich in lipoid. Several consultant pathologists considered this tumor to be an adrenal tumor or hypernephroma of the ovary.

One of the most difficult variations is illustrated by O.T.R. 176 (Fig. 3, *A*). This section would be interpreted as a glandular type of adenocarcinoma. In the same tumor, however, numerous variations occurred. Definite granulosa cells with cystic liquefaction, resembling those illustrated, could be demonstrated (Fig. 1, *B*). Many small clusters and rosette forms were observed (Fig. 3, *B*). In addition, anaplastic sarcomatous areas (Fig. 7, *D*) made this tumor difficult to classify. The following diagnoses were made: (1) granulosa-theca-cell tumor; (2) teratoma; (3) carcinosarcoma; (4) serous cystadenocarcinoma; (5) embryonal carcinoma; (6) combined tumor. It should be pointed out that we have avoided including papillary types of structures in this treatise as a type of feminizing mesenchymoma. The possibility exists, however, that this tumor,

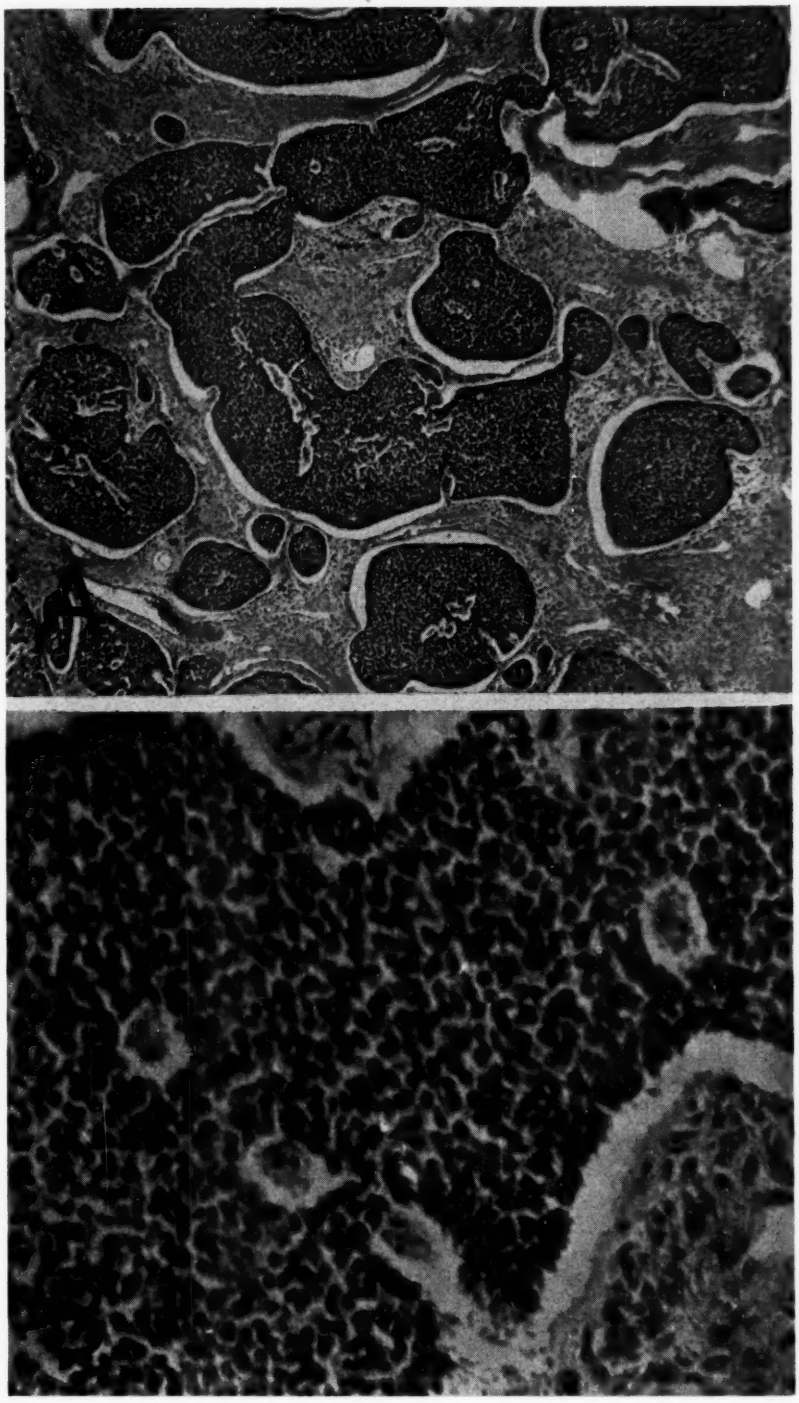

Fig. 1.—*A*, O.T.R. 132. Photomicrograph of a typical feminizing mesenchymoma with a microfolliculoid pattern with some features also of a cylindromatous type. (Hematoxylin and eosin. ×100; reduced ¼.)

B, O.T.R. 132. Photomicrograph of the same tumor as in *A*, illustrating the basic arrangement of the granulosa cells in small clusters or rosettes around a central lumen. (Hematoxylin and eosin. ×300; reduced ¼.)

(O.T.R. 176) may represent the widest spectrum of polymorphism of the feminizing mesenchymomas. This patient died on the sixth postoperative day. No autopsy was obtained.

The fourth debatable tumor, O.T.R. 32 (Fig. 4, *A*) illustrates the problem of differentiation between the histology of arrhenoblastoma and feminizing mesenchymomas. The diagnosis often depends on the appearances of the

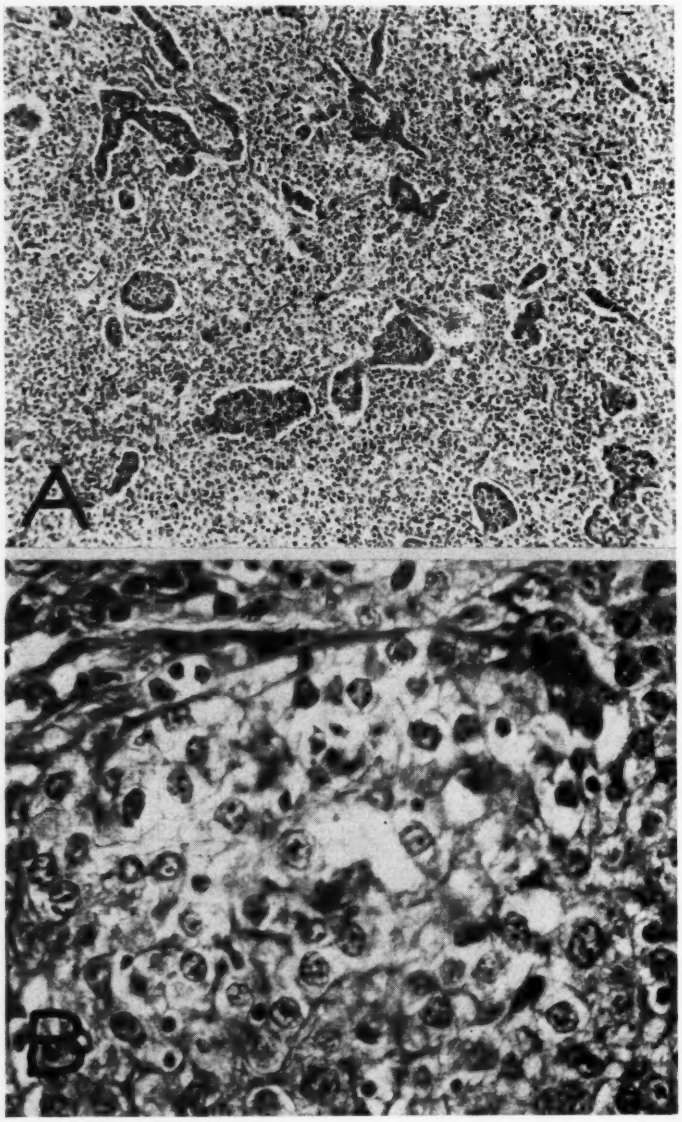

Fig. 2.—*A*, O.T.R. 199. Photomicrograph of a feminizing mesenchymoma which was confused with a Brenner tumor showing patchy luteinization with islands of granulosa cells. (Hematoxylin and eosin. ×100; reduced ¼.)

B, O.T.R. 13. Photomicrograph of a feminizing mesenchymoma with marked lutenization. Folliculoma lipidique. Often confused with an adrenal rest or hypernephroma. Hematoxylin and eosin. ×500; reduced ¼.)

"tubules." In the granulosal tumors the cells are arranged in an antipodal position with the nuclei of the inner layer closer to the central lumen, while the nuclei of the outer layer tend toward the periphery. The cells of the tubules of arrhenoblastoma possess double columns and have their nuclei at right angles to the long axis of the columns. This tumor in other areas than that portrayed by the photomicrographs presented typical microfolliculoid patterns.

The fifth debatable tumor illustrates one of the difficulties of registry pathology. This tumor, O.T.R. 251, was apparently not well fixed in preparation and since only one or two blocks were sent in, the appearance of the tumor

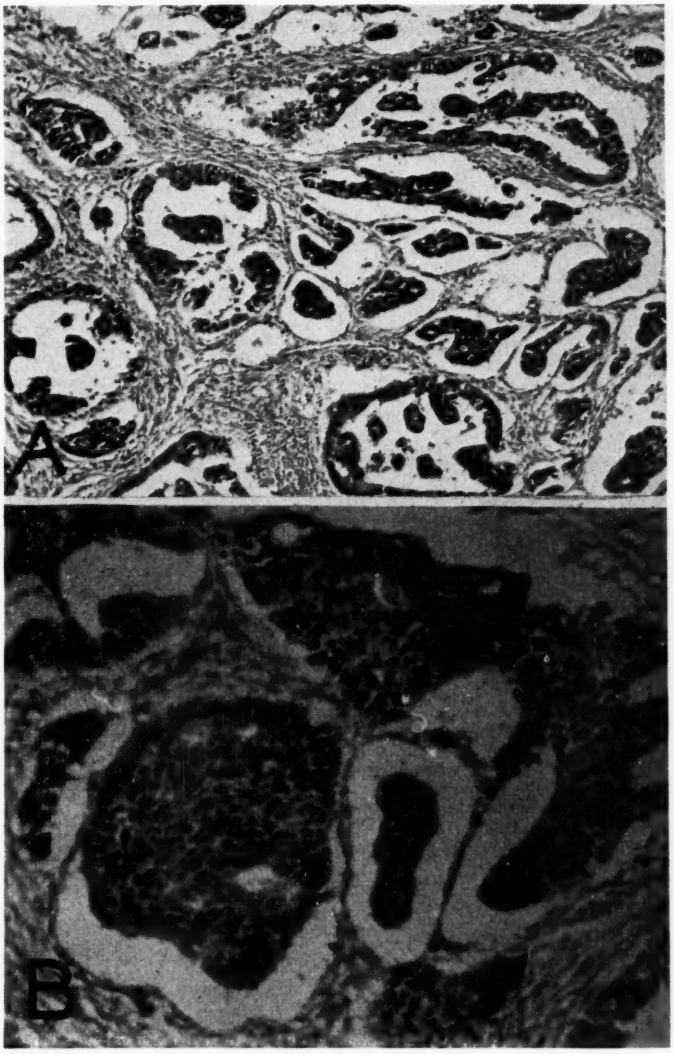

Fig. 3.—*A*, O.T.R. 176. Photomicrograph of an isolated area of a feminizing mesenchymoma which simulates an adenocarcinoma of the ovary. In the same slide typical microfolliculoid patterns were also present. (Hematoxylin and eosin. ×160; reduced ¼.)

B, O.T.R. 176. Photomicrograph of another area of the same tumor as in *A*, with small groups and clusters of granulosa cells. (Hematoxylin and eosin. ×300; reduced ¼.)

(Fig. 4, *B*) could be confused with that of a dysgerminoma or a reticulum-cell sarcoma. In all fairness it might not be a granulosa-cell tumor. Several experts classified it as a partially luteinized granulosa-cell tumor. The patient is alive and well 9 years after the original removal of the tumor.

The sixth and final debatable tumor, O.T.R. 396 (Fig. 5, *A*), consisted of numerous areas of ovarian stroma and necrosis with some angiomatous structures. In other areas, however, particularly over the surface of the tumor, a more characteristic granulosa-cell pattern was present (Fig. 5, *B*). The stroma of the tumor also contained numerous polyhedral cells resembling thecal cells. Many experts consider this tumor to be an angioma, but Dr. Novak interpreted the tumor as a feminizing mesenchymoma.

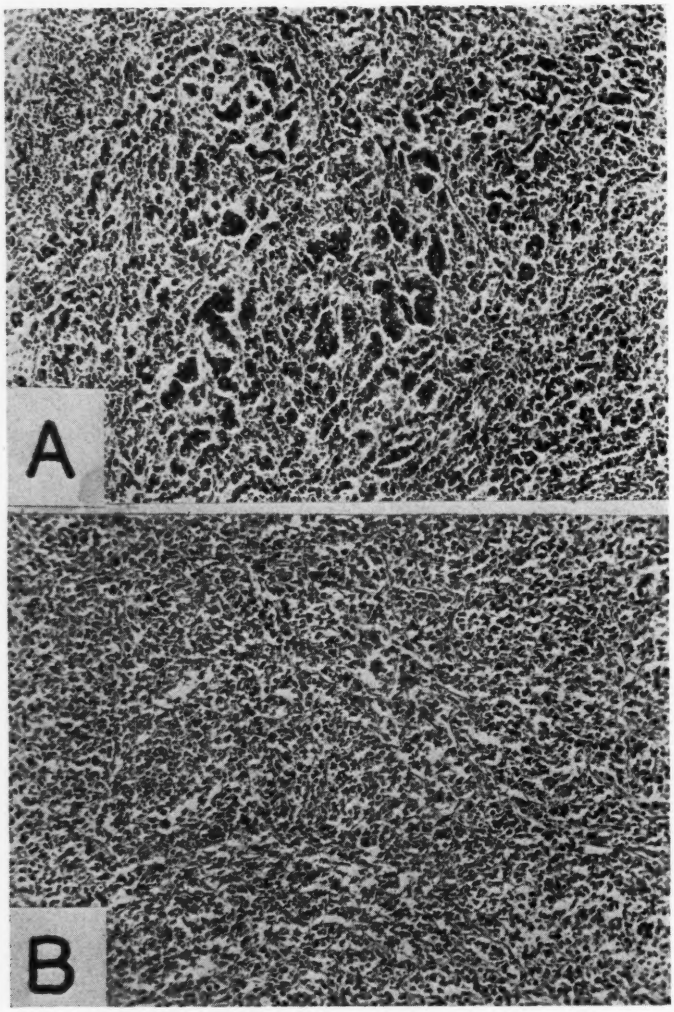

Fig. 4.—*A*, O.T.R. 32. Photomicrograph of a feminizing mesenchymoma which in some areas simulated the structure of arrhenoblastoma. (Hematoxylin and eosin. ×100; reduced ¼.)

B, O.T.R. 251. Photomicrograph of a degenerating feminizing mesenchymoma which has the appearance of a dysgerminoma. (Hematoxylin and eosin. ×100; reduced ¼.)

The previous six tumors represent the extreme polymorphism which may be possible in the feminizing mesenchymomas. We are not completely satisfied that all of the debatable cases are proved beyond any reasonable doubts. Cases 13, 32, and 199 appear to be on stronger grounds than cases 176, 251, and 396. These cases will again be referred to in the section on five-year survival and mortality. It would have been easier and perhaps wiser to have deleted these few cases from this study, but in the spirit of this report it was deemed necessary to present an honest evaluation of the pathological diagnoses made by the different members of the committee.

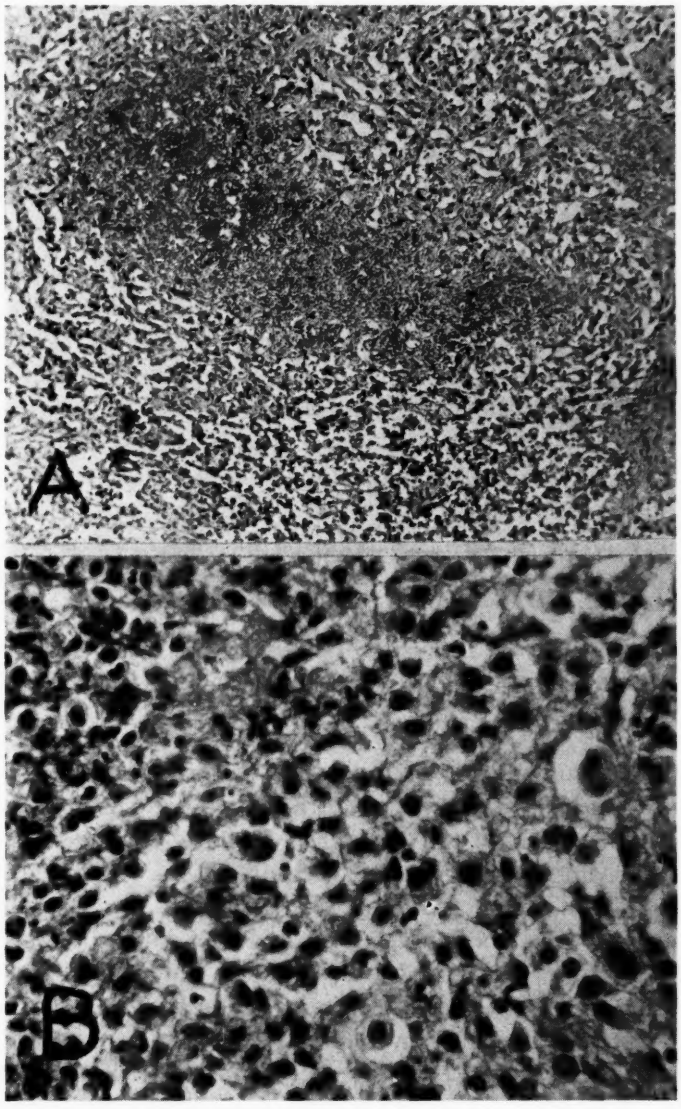

Fig. 5.—*A*, O.T.R. 396. Photomicrograph of a feminizing mesenchymoma with an angiomatous appearance. (Hematoxylin and eosin. ×100; reduced ¼.)

B, O.T.R. 176. Another area of the same tumor as in Fig. 3, *A* with a more characteristic granulosa-cell pattern. (Hematoxylin and eosin. ×500; reduced ¼.)

Clinical Features of Feminizing Mesenchymomas

This report would indicate that the feminizing mesenchymomas are not very uncommon. Novak states that they comprise about 10 per cent of all solid malignant tumors. In this study the feminizing mesenchymomas comprised almost 40 per cent of the solid malignant tumors submitted to the registry. It is difficult to secure data as to what percentage of all ovarian neoplasms are feminizing mesenchymomas. Falls and others describe incidences of 1 to 4 per cent. Fifteen women, or 14 per cent of our series, are Negroes. These tumors can occur at any age, before puberty, during the reproductive epoch, or after the menopause. Hodgson and Dockerty found the average age at the time of detection of granulosa-cell tumors as 52 years. The age distribution of 106 cases in which the age was known is described in Fig. 6. There were no significant differences in the age distribution of granulosa-cell, granulosa-theca, or theca-cell tumors. The ages varied from 7 months to 78 years of age. The average age for the entire group was 45 years, the median age was 50 years, and the modal age between 50 and 55 years. In other words, over 50 per cent of our patients were over 50 years of age.

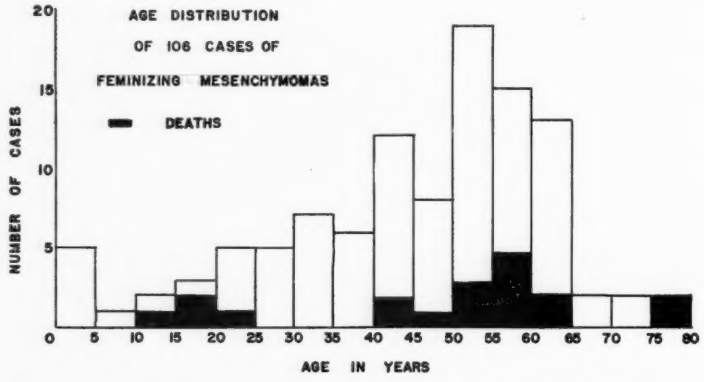

Fig. 6.—Graph illustrating the age distribution of 106 cases of feminizing mesenchymomas. In one case the age of the patient was unknown. Deaths are represented by black areas.

As is generally understood, granulosa-cell tumors are not as clinically active during the reproductive life of a woman as in the prepubertal and postmenopausal periods of their lives. In this series 6 cases occurred in girls under 10 years of age, 2 of which cases occurred with precocious puberty, breast enlargement, growth of pubic hair, and in 1 case precocious menses at the age of 3 years. One of the girls was only 1 year old and had a thecoma. Giardini claimed that thecomas were never observed before puberty. This case has been previously reported by Gordon and Marvin in 1951. These authors surveyed 126 theca-cell tumors described in the literature and were unable to find a similar thecoma in the prepubertal age group. This little girl infant had enlarged breasts, pubic hair, a slightly enlarged uterus with some vaginal bleeding. In the reproductive years the hyperestrinism may be associated with normal menstruation, increased menstruation, or periods of amenorrhea. Eight of our

cases, or 7.5 per cent, had amenorrhea varying from 5 months to 24 months in duration. The histological picture varied from the diffuse luteinized type of tumor in 4 cases to the simple folliculoid type. Five of the 8 women resumed normal menstruation shortly after removal of the tumor. Two others had hysterectomy and in one case the postoperative menstrual history is unknown. The menstrual changes in 107 cases of ovarian mesenchymomas were as shown in Table VII.

TABLE VII

	GRANULOSA-CELL TUMORS	GRANULOSA-THECOMAS	THECOMAS	TOTAL
Precocious puberty	2	0	0	2
Normal premenopausal	6	1	0	7
Menometrorrhagia	16	5	2	23
Oligomenorrhea	0	0	1	1
Amenorrhea	5	3	0	8
Pregnant	3	0	1	4
Menopausal bleeding	11	3	2	16
Postmenopausal bleeding	22	6	4	32
Previous hysterectomy	5	1	1	7
No data	5	0	2	7
Total	75	19	13	107

The data in Table VII would indicate that the relative incidence of abnormal bleeding was approximately the same for the granulosa-cell, granulosa-theca-cell and theca-cell tumors. When granulosa-cell tumors develop in the postmenopausal years, the endometrium usually exhibits proliferative activity. This picture is often of the "Swiss-cheese" variety. At first this finding was often thought to be some evidence for an ovarian mesenchymoma, but other data and our own would not support this premise. The associated endometrial pathology in 107 cases of ovarian mesenchymomas is given in Table VIII.

TABLE VIII

	GRANULOSA-CELL TUMORS	GRANULOSA-THECOMAS	THECOMAS	TOTAL
Nonsecretory	7	1	2	10
Secretory	2	0	0	2
Swiss-cheese hyperplasia	6	2	1	9
Benign polyp	1	1	0	2
Postmenopausal atrophic	7	0	0	7
Postmenopausal hyperplasia	5	2	2	9
Adenocarcinoma	2	1	0	3
Metastatic tumor	2	1	0	3
No data	43	11	8	62
Total	75	19	13	107

It would also be evident from these data that granulosa-cell tumors and thecomas have about the same estrogenic activity. An interesting feature was the presence of 3 cases of adenocarcinoma of the endometrium. Ingram and Novak collected 54 cases of combined feminizing mesenchymoma and adenocarcinoma of the endometrium. Four of the 66 tumors (or 6 per cent) had this relationship as compared to 2.8 per cent in this series of feminizing mesenchymomas. Recently, Corbet, Miller, and Tod have surveyed the literature and

have increased the number of cases of endometrial carcinoma associated with feminizing tumors of the ovary to a total of 70. Larsson and Olson tried to demonstrate that although granulosa-cell tumors are more frequent than thecomas, yet 28 thecomas have been reported in association with adenocarcinoma of the endometrium, whereas only 22 granulosa-cell tumors have been similarly reported. Woll and his associates reported 17 cases of these combined tumors and concluded that thecomas were nine times more common than in their control series. Our small series of thecomas do not help substantiate the idea that thecoma exerts a stronger carcinogenic effect on the endometrium than does granulosa-cell carcinoma.

Three of the 107 patients also had breast carcinoma. The endocrine nature of both types of tumors might suggest a possible relationship. There were 13 cases with ascites, but only 1 of these had pleural effusion. Four patients were pregnant at the time the tumor was discovered, which at least indicates that this group of tumors does not inhibit ovulation in all cases. Dockerty states that the presence of an intrauterine pregnancy with granulosa-cell tumor is very rare. Spencer and Hollenbeck were unable to find in the American literature a case other than the one presented by them of a third trimester pregnancy associated with a large granulosa-cell tumor. Hamilton and Higgins also reported a granulosa-cell tumor removed in the sixteenth week of pregnancy followed by successful term delivery. In a recent review of the literature, Diddle and O'Connor collected 37 cases of feminizing mesenchymomas in which there was some relationship to pregnancy. In 12 patients in whom pregnancy was coexistent with the tumor, 6 went on to term, one aborted, and in 5 the outcome was unknown. In 15 other women, 16 pregnancies occurred after removal of the tumor with 6 viable babies, 2 nonviable fetuses, and an unknown outcome for 8 others. These authors deduced that feminizing mesenchymomas produced abortion tendencies and sterility previous to their removal.

Of the 4 cases of feminizing mesenchymoma associated with pregnancy in this study, one patient died at the time of delivery with rupture of the tumor and massive intraperitoneal hemorrhage. In a second case, the tumor was discovered in the second month of pregnancy at which time the ovarian neoplasm was removed and followed by successful term delivery. The third patient was delivered by cesarean section and because of bilateral ovarian masses both ovaries were removed. This patient is alive and well and free of recurrence seven years following surgery. The fourth patient whose pregnancy was associated with a granulosa-cell tumor delivered a full-term infant. At the time of delivery a large ovarian mass was palpated but surgery was delayed for eight months, at which time a large granulosa-cell tumor was removed by simple oophorectomy. This patient is alive and well five years later and also has had a second live child subsequently.

Hirsutism was described in 5 of the cases. In Table IX the age, type of tumor, and location of hirsutism are described.

Perhaps this is a paradoxical symptom of a feminizing tumor, and to be sure its exact mechanism of production is unknown. The importance of this symptom cannot be overlooked because it appeared to influence several of the

consulting pathologists to change their diagnoses from feminizing mesenchymoma to arrhenoblastoma even when rather typical histological characteristics such as microfolliculoid structures were present. One of our patients with feminizing mesenchymoma associated with pregnancy developed hirsutism and a husky voice. Although hirsutism during pregnancy has been described by Stoddard without concomitant hair-growth-producing neoplasms, it has also been described by Alexander and Beresford as occurring with bilateral theca-cell tumors. Diddle and O'Connor also reviewed three cases of thecoma associated with pregnancy with masculinizing signs. It must be kept in mind that terminology and definition may be partially responsible for the failure of certain experts to accept these previously reported cases of masculinization associated with feminizing mesenchymomas. In general, the clinical features of these 107 cases of feminizing mesenchymomas reported tended to follow the previously described patterns of the literature.

TABLE IX

O.T.R. NUMBER	AGE	TYPE OF TUMOR	HIRSUTISM LOCATION	POSTOPERATIVE REGRESSION OF HIRSUTISM
199	16	Luteinized granulosa-theca	Mustache, enlarged clitoris	Regressed
256	53	Granulosa-theca	Face and back, one year's duration	Disappeared
267	38	Theca-cell	Shaves, back and abdomen	Decreased
318	25	Mixed	During pregnancy, abdomen	Decreased
338	70	Tubular pseudo-adenomatous	Mustache, baldness	Unchanged

Mortality and Survival-Rate Studies

Some of the most important data to be obtained from this study of feminizing mesenchymomas are the follow-up studies. It should be pointed out that, although five-year survival rates are being reported, these types of tumors have been demonstrated by Compton, Jones, and Te Linde to have recurrences as long as 18 to 20 years after the initial surgery.

It was possible to secure follow-up reports of five years or more in 96 of the 107 cases. Of 11 cases without five-year follow-up periods, 9 cases were followed two to four years and then lost sight of, and 2 cases had no follow-up studies at all. Of the 96 cases with complete five-year follow-up studies the results were as follows:

Living and well after 5 years	74
Living with recurrence	2
Total living and well after 5 years	76 (79.2%)
Total dead in first five years	20 (20.8%)
Total dead in first seven years	22 (22.9%)

For those readers who are unable to accept the debatable cases, we have calculated the five-year mortality rate as 21.1 per cent if all 6 cases are deleted or 20.4 per cent if only cases O.T.R. 176, 251, and 396 are deleted. The literature

on the malignancy and five-year survival rates is very difficult to interpret. In an attempt to compare our findings with previous data, however, Table X was prepared.

TABLE X

YEAR	AUTHOR	NUMBER OF CASES	PER CENT MALIGNANT	FIVE-YEAR MORTALITY PER CENT
1934	Novak and Brawner	32	28.1	--
1937	Compton	115 (review)	29.5	--
1942	Henderson	30	3.3	--
1945	Hodgson, Dockerty, and Mussey	62	--	4.8
1949	Allan and Hertig	37	30.0	--
1950	Haines and Jackson	40	53.0	45.0
1950	Kottmeier	70	--	8.5
1951	Henderson	40	35.0	43.3
1953	Duckett, Davis, and Fetter	17	--	35.6
1954	Ovarian Tumor Registry	96	25.0	20.8

Perhaps at this point it might be proper to discuss the 20 deaths which occurred in 96 women followed five or more years after surgery. In Table XI details of the fatal cases are listed for the reader's convenience. The time of death following diagnosis may be tabulated as follows:

Deaths in immediate postoperative period	3
Deaths, patients untreated (autopsy diagnosis)	2
Deaths during first year	9
Deaths during second year	3
Deaths during third year	3
Deaths during fourth year	0
Deaths during fifth year	0
Total	20

In addition to these, 2 additional deaths have occurred 7 years following surgery which would raise our seven-year mortality to 22.9 per cent at the present time. Two women also living with recurrences would set the malignancy of feminizing mesenchymomas at 25 per cent.

Two of the 20 patients died untreated with massive intraperitoneal hemorrhage. French has reported two cases of rupture of granulosa-cell tumors with 500 c.c. and 1,500 c.c. of blood in the peritoneal cavity at the time of laparotomy, and was able to collect twenty-five similar cases in the previous literature. Von Friesen also found 7 cases in Sweden of extensive intra-abdominal hemorrhage. Bogle reported a case in 1949 of a serious abdominal emergency due to a ruptured feminizing mesenchymoma with severe intraperitoneal bleeding. Three other deaths occurred in the immediate postoperative period. These deaths emphasize the need for meticulous preoperative and postoperative care associated with the surgery of ovarian neoplasms. The immediate causes of the 20 deaths were as follows:

Metastases	13
Peritonitis	2
Rupture of tumor	2
Cardiac failure	1
Carcinoma of breast	1
Unknown	1
Total	20

Perusal of Table XI revealed that four of the deaths were in women 14, 18, 19, and 22 years of age and the remaining 14 deaths occurred in women over 42 years of age. The duration of symptoms varied from 0 to 24 months with an average of 5.2 months. Three women among the 20 who died, however, were entirely asymptomatic. Ten of these patients had a mass or pain in the lower abdomen as their presenting complaint.

The extent of the disease at the time of operation may also be important. Fourteen of the patients who died, or 70 per cent, had extension of the tumor beyond the ovary at the time initial surgery was performed. Eleven of 12 women over 50 years of age who died also had extension beyond the ovary. In 92 cases in which the extent of the disease was definitely stated at the time of operation and followed at least five years after operation the prognosis was as follows:

EXTENT OF TUMOR	CASES	DEATHS IN FIVE YEARS	PER CENT MORTALITY
Confined to ovary	71	8	11.2
Extension beyond ovary	21	9	42.8

From these data it appears that involvement of the peritoneum and adjacent abdominal structures would indicate a bad prognosis. On the other hand it is interesting that 11 patients of 21 with extension beyond the ovary did survive more than five years following operation, and in 6 cases of this group only simple oophorectomy was performed. This would encourage the removal of the primary tumor in seemingly hopeless cases.

If we consider the predominant cell type, the mortality can be illustrated as follows:

HISTOLOGIC TYPE			
Granulosa cell	74	17	22.9%
Granulosa theca	13	1*	7.6%
Theca cell	9	2†	22.0%
Total	96	20	20.8%

From these data, no great difference in prognosis according to cell type appeared to exist; but, unfortunately, 2 deaths in the granulosa-theca cell and theca-cell types were due to torsion and hemorrhagic complications rather than to metastasis. The thecoma group which is said to be least malignant, however, had 1 case in which the tumor was Grade IV by histologic criteria with extensive metastases at the time of surgery. In the previous literature, Carter, Dahlin, and Pratt, and Kleitsman have calculated the mortality with thecomas to vary from 4 to 5 per cent. At the present time only 5 established cases of malignancy in thecomas have been reported. This has been increased to 6 cases by the recent report of Rogers, Gordon, and Marsh.

Histopathologic Grading and Survival

The degree of malignancy of a tumor is dependent upon several factors such as structure, mode and rates of growth, metastases, and final clinical results. In one attempt to probe structural changes as an aid to the clinician in prognosis

*One patient died of hemorrhage following rupture of tumor.
†One patient died of hemorrhage following rupture of tumor during delivery.

TABLE XI. ANALYSIS OF 20 DEATHS ASSOCIATED WITH 96 FEMINIZING MESENCHYMOMAS OF THE OVARY DURING THE FIVE-YEAR SURVIVAL PERIOD, AMERICAN GYNECOLOGICAL SOCIETY OVARIAN TUMOR REGISTRY

O.T.R. NUMBER	AGE	SYMPTOMS AND DURATION	EXTENSION OF TUMOR	SURGERY	POSTOPERATIVE X-RAY	TYPE OF TUMOR	GRADE OF MALIGNANCY	FINAL CAUSE OF DEATH
Deaths in Immediate Postoperative Period (30 Days).—								
50	53	Abdominal mass 5 months	Stomach and intestines, uterus	Bilateral salpingo-oophorectomy, hysterectomy	None	Micro and diffuse	I	Died 26th day, peritonitis
176	75	Abdominal pain 4 months	Bladder, sigmoid	Bilateral salpingo-oophorectomy, hysterectomy	None	Mixed	IV	Died 1 week postop. peritonitis?
231	63	Abdominal mass 6 months	None	Bilateral salpingo-oophorectomy, hysterectomy	None	Tubular	III	Died 1 week postop. unknown
376	44	Bleeding 6 months	None	None	None	Granulosa-thecoma	I	Ruptured varix over surface of tumor
478	18	None Pregnancy	None	Delivery stillborn infant	None	Thecoma	II	Ruptured tumor. Hemoperitoneum 3,000 c.c.
Deaths During First Year.—								
38	78	Abdominal mass 4 months	Omentum, bowel, bladder	Right oophorectomy	None	Thecoma	IV	Died of metastases
49	58	Bleeding 3 months	Sigmoid, uterus	Hysterectomy bilateral salpingo-oophorectomy resection sigmoid	X-ray therapy	Cylindromatous	III	Died of metastases
51	52	Abdominal mass 9 months	Bilateral pelvic structures	Bilateral salpingo-oophorectomy	X-ray therapy	Mixed	II	Died of metastases

73	45	Pain 1 month	Bilateral omentum, parametrium	Bilateral salpingo-oophorectomy	None	Cylindromatous	II	Metastases
84	55	Abdominal mass 2 months	Bilateral omentum, cul-de-sac	Hysterectomy, bilateral salpingo-oophorectomy	X-ray therapy	Tubular	III	Metastases
108	22	Urinary 6 months	None	Salpingo-oophorectomy	X-ray therapy	Mixed type	III	Metastases
169	55	Bleeding 6 weeks	Bilateral, omentum, colon, bladder	Hysterectomy, bilateral salpingo-oophorectomy	None	Mixed	III	Metastases
395	14	Mass 6 weeks	None	Unilateral salpingo-oophorectomy	None	Sarcoma	III	Metastases
439	-	-	Omental metastases		None	Sarcoma	III	Ruptured viscus, peritonitis
Deaths During Second Year.—								
155	19	Menorrhagia 5 months	Peritoneum	Unilateral salpingo-oophorectomy	None	Micro-folliculoid	III	Metastases
240	64	Distention 12 months	Sigmoid	Bilateral salpingo-oophorectomy, hysterectomy	X-ray	Diffuse and sarcoma	III	Metastases
275	55	Bleeding 24 months	Peritoneal implants	Unilateral salpingo-oophorectomy	None	Cylindromatous	I	Metastases
Deaths During Third Year.—								
99	55	Pain 12 months	Bilateral, uterus, peritoneum	Hysterectomy, bilateral salpingo-oophorectomy	X-ray, radon seeds	Cylindromatous	II	Metastases
260	51	Routine checkup	Omentum, intestines, cul-de-sac	Left oophorectomy	X-ray	Mixed	I	Metastases
492	42	Carcinoma of breast	To control Ca. of breast, ovary removed	Left oophorectomy, hysterectomy	None	Mixed	IV	Died of carcinoma of breast

regarding the feminizing mesenchymomas, histologic grading of the tumors was attempted. Many outstanding pathologists have nò use for grading and heartily condemn the procedure. With reluctance, however, we decided to give grading at least one chance. Broders has been the leading exponent of grading neoplasms of other organs. Taylor has applied grading to ovarian tumors with some success. C. W. Taylor of England applied grading methods to primary carcinoma of the ovary and reported five-year survivals of 65.5 per cent with Grade I as compared to only 2.4 per cent with Grade III. Allan and Hertig have used grading with carcinoma of the ovary. Their system has been to consider the well-differentiated tumors as Grade I, the wildly anaplastic tumors with a profusion of mitoses and bizarre cells were denoted as Grade III. Falls and his coworkers feel that distinct variation in the size and shape of nuclei, increased number of mitotic figures, and invasion of the capsule by the tumor are criteria for the diagnosis of malignancy in a granulosa-cell tumor.

With this background, each of us reviewed the slides and gave each case a grade from I to IV. In tumors with a wide variation in pattern and cell changes the most malignant areas were accepted for grading. Arbitrarily, the classification concept of Broders was adopted with Grade I designating those cases with 25 per cent or less anaplastic cells; Grade II, cases with 25 to 50 per cent anaplastic cells; Grade III, 50 to 75 per cent anaplastic cells; and Grade IV, more than 75 per cent anaplastic cells. The various types are illustrated with photomicrographs (Fig. 7, *A-D*). Comparisons of the independent grading of each author were then tabulated, and only minor variations between cases were observed. Usually, one grade of difference occurred, and in no instance was a Grade I mistaken for a Grade IV and vice versa. We then grouped the cases according to those dead and followed at least five years according to the histologic degree of malignancy as follows:

HISTOLOGIC GRADE	NO. OF CASES	DEATHS	PER CENT MORTALITY
I	42	4	9.5
II	35	4	11.4
III	15	9	60.0
IV	4	3	75.0
Total	96	20	20.8

This tabulation would indicate that it is of some value for the pathologist to incorporate some of the principles of grading in an effort to ascertain the prognosis of the patient with a feminizing mesenchymoma. A look at Table XI, however, indicates that grading alone is not infallible since in several instances delayed metastases occurred even though the original tumor was Grade I. As previously described, 14 of 20 patients who died had extension beyond the ovary at the time of their initial surgery. In 6 cases, no extension was present. The histological grades in these 6 cases were as follows:

Grade I	1 case with rupture of tumor and hemoperitoneum
Grade II	1 case with rupture of tumor and hemoperitoneum
Grade III	3 cases
Grade IV	1 case

From this it appeared that in cases without extension grading was of some significance to the prognosis of the patient.

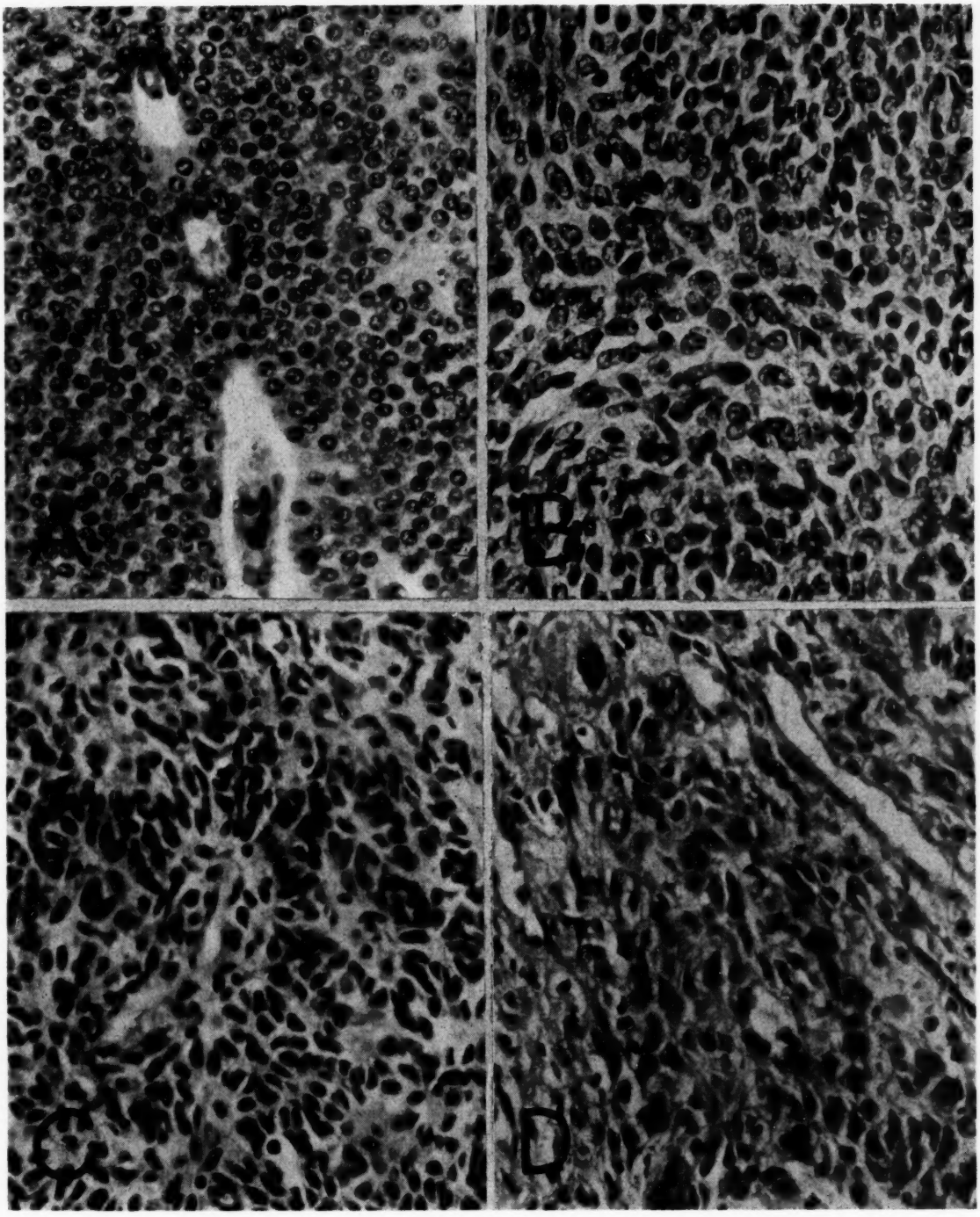

Fig. 7.—*A*, O.T.R. 275. Feminizing mesenchymoma, Grade I malignancy. Less than 25 per cent anaplastic cells. (Hematoxylin and eosin. ×500; reduced ¼.)

B, O.T.R. 30. Feminizing mesenchymoma, Grade II malignancy. Twenty-five to 50 per cent anaplastic cells. (Hematoxylin and eosin. ×500; reduced ¼.)

C, O.T.R. 155. Feminizing mesenchymoma, Grade III malignancy. Fifty to 75 per cent anaplastic cells. (Hematoxylin and eosin. ×500; reduced ¼.)

D, O.T.R. 176. Feminizing mesenchymoma, Grade IV malignancy. More than 75 per cent anaplastic cells. (Hematoxylin and eosin. ×500; reduced ¼.)

Treatment

The method of treatment of 96 cases of feminizing mesenchymoma varied greatly. In Table XII an attempt was made to list the type of treatment given and the resultant five-year mortality rates.

TABLE XII

TYPE OF TREATMENT	NO. OF CASES	DEATHS	PER CENT MORTALITY
Unilateral salpingo-oophorectomy	19	6	31.6
Bilateral salpingo-oophorectomy	36	2	5.5
Hysterectomy + salpingo-oophorectomy	27	5	18.5
Hysterectomy + salpingo-oophorectomy + postoperative x-ray	11	4	36.3
No treatment	2	2	—
No data	1	1	—
Total	96	20	

This table merely illustrates the multiple therapeutic procedures that are used. Most previous authors have advocated that conservative procedures should be carried out in young women and radical procedures in the older group. Referring to Table XI, it should be pointed out that only 3 of the 20 deaths occurred in women under 40 years of age. One of these young women died during delivery of a stillborn infant from rupture of the tumor. The other two patients had Grade III tumors and were treated with unilateral salpingo-oophorectomy. One had extension to the peritoneum, and the other was without extension. In these three cases, however, we felt that inadequate surgery (simple oophorectomy) was contributory to the fatal outcome. In all fairness, however, these 3 were young women, aged 14 to 22 years, and conservatism in pelvic surgery in women of this age is a gynecologic keynote. It is noteworthy that 6 of the patients who died had had previous pelvic surgery, including unilateral oophorectomy. Perhaps this is a sampling error, but the incidence does seem far above the incidence of women with previous pelvic surgery in general. One could only guess as to whether this is of etiological importance. On the other hand, one might value the clinical observation of the frequency of ovarian cancer in women with previous pelvic surgery. These data are quite contrary to the usual gynecologic teaching that unilateral oophorectomy reduces by 50 per cent a woman's chances of developing ovarian carcinoma. Henderson in a report to this society advocated more radical surgery in the treatment of granulosa-cell tumors. Five of his patients who developed recurrences in less than five years had been treated by simple oophorectomy. In our study, 4 of 12 women who died in the age group over 50 had simple oophorectomy. Therefore, it may be wise even in younger women with tumors that have adhesions to adjacent viscera or actual metastases to carry out complete removal of the pelvic genital organs.

It is impossible from this type of study to discuss the use of x-ray therapy since only 11 of 96 patients received postoperative x-ray, except to state that it appeared to be used in the most desperate cases. Among the 20 fatal cases, x-ray therapy was used only once in 7 patients under 50 years of age and in

6 of 12 patients over 50 years of age who died. Kottmeier of the Radiumhemmet in Stockholm emphasizes the use of roentgen therapy in all cases of the sarcomatous type of granulosa-cell tumor and in those cases in which the tumor has ruptured. This group believes that the granulosa-cell tumor is often radiosensitive. It may be interesting at this point to mention that these 107 tumors were submitted from 23 states and 6 foreign countries. Ninety-seven different surgeons executed the treatment in this study. In spite of the numerous surgeons involved in this study, there appeared to be some agreement that surgical treatment is the method of choice for feminizing mesenchymomas. Radiation therapy may be of some help, particularly in cases with widespread extension of the tumor.

Conclusions

Approximately 1,000 ovarian tumors have been collected in the Ovarian Tumor Registry sponsored by The American Gynecological Society. In 1954, the first 500 cases have completed a five-year follow-up period, and among these tumors 107, or 21.4 per cent, were feminizing mesenchymomas of the ovary. The slides and histories were submitted to the five consulting gynecologic pathologists of the Ovarian Tumor Committee. Statistical analysis of 463 independent diagnoses made by these consultants revealed that 343, or 74 per cent, were in agreement with the diagnosis of feminizing mesenchymoma. Six of the most debatable tumors are illustrated and discussed in some detail.

Many clinical features of these tumors are evaluated, but, in general, the 107 cases tended to follow the generally accepted concepts described in the previous literature. Of primary interest are the five-year survivals. Only 96 of the original 107 cases have been followed 5 years or more since the primary operation. Of 11 cases without five-year follow-up periods, 9 cases were followed two to four years and then lost sight of, and two cases had no follow-up studies at all. This series of cases is the largest group of feminizing mesenchymomas reported in the literature with five-year follow-up studies. Of these cases, 76 patients, or 79.2 per cent, are living and 20, or 20.8 per cent, are dead within five years. Two additional deaths occurred 7 years following surgery which raises the seven-year mortality to 22.9 per cent. Another 2 women are still alive with recurrences, which sets the malignancy of feminizing mesenchymomas at 25 per cent.

The factor which most affected prognosis was the gross stage of the disease at the time of operation. When the neoplasm was confined to one ovary, the five-year mortality was 11.2 per cent as compared to a mortality of 42.8 per cent in those cases with extension to adjacent structures. The next most important factor was the histological grade of the tumor, in that Grade I had a five-year mortality of 9.5 per cent as compared with a 75 per cent mortality in Grade IV.

The methods of treatment were extremely variable. There was some evidence, however, that complete evisceration of the pelvic genital tract was important in patients in the menopausal age group. The role of the x-ray could not be ascertained.

We wish to thank the American Gynecological Society for the privileges extended in preparation of this report. We are particularly indebted to Dr. Emil Novak, the chairman of the Ovarian Tumor Registry, and the members of the committee, Drs. Herbert E. Traut, George H. Gardner, Karl H. Martzloff, and Robert Faulkner. The services of Miss Eva Hildebrandt were greatly appreciated in the preparation of slides and numerous follow-up data. Special consideration should be given to the 97 gynecologists and pathologists from 23 states and 6 foreign countries who have proved that a cooperative study of this type is possible and have faithfully submitted their cases and follow-up data from year to year.

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Discussion

DR. ARTHUR T. HERTIG, Boston, Mass.—It is a very difficult job to discuss in five minutes this very important and exhaustive paper that has been prepared and presented by these careful workers on a group of tumors which has such a variety of histologic types. I think it is well to point out that this type of tumor *should* have a wide variety of histologic types for the simple reason that involved are the granulosa cell and the theca interna, either of which may be luteinized. The theca externa elements are also present and in variable degrees of activity. There may be various admixtures of all three of these elements, and there may be variable degrees of malignancy in any or all of them. I suppose, therefore, that theoretically and practically it is not only the most complicated ovarian tumor in its histogenesis but among the most interesting, and, as I tell the medical students, the most glamorous.

In reporting on this large series of tumors from a consultation practice, one gets the idea that these are very common tumors, but it might be well to point out that the approximate occurrence rate of granulosa-cell or theca-cell tumor is of the order of about 2 per cent of all ovarian tumors. In some 740 consultation specimens covering all sorts of gynecologic pathology that have been sent to me at the Free Hospital in six years, there were 40 of these tumors, or an incidence of 5 per cent of one's consultation practice. The 43 cases that were from the files of the Free Hospital for Women alone, covering a period of about 40 years, indicate some of the ordinary variation of morphology in a selected group —selected only because they happened to come to a gynecologic hospital—and I thought it might be interesting to show some of these morphologic variations.

The first slide is a diagram of a normal ovary that depicts the elements of the tumor that we are considering: the granulosa cells, the theca interna and externa, and the normal cortical stroma.

Here illustrated is a typical pure granulosa-cell tumor of the folliculoid variety with some thecal stroma. In this case it arose following unwitting irradiation of a patient who was allowed to sit with her mother while the latter was being irradiated for carcinoma of the breast.

Here illustrated is a malignant variant of the granulosa-cell tumor, which we call a luteoma. It is one of the few pure luteomas we have seen. It was grossly a brilliant yellow

tumor and was a carcinoma morphologically and clinically. The patient died in two years of widespread metastases. We think it is a luteinized granulosa-cell tumor because it has a trabecular pattern and the cells are enlarged and appear to be what we call luteinized.

Here illustrated is the only unequivocal luteoma I have ever seen. It occurred in a 24-year-old pregnant patient, six weeks from term, who had a cesarean section because of eclampsia. Here are the obvious granulosa cells and here the K cells which are histochemically the source of ketosteroids. This is apparently a benign tumor, although we have no follow-up data on her.

The next is an example of a mixed variety. It is a question of whether to call it a granulosa-cell tumor or thecoma. One section of the tumor showed a partially luteinizing area. We did reticulum stains on this and showed the cells to be of thecal origin. One of the classic papers on this group of tumors is the one by Traut and Marchetti who pointed out that theca cells had reticulum around them and granulosa cells did not. This case of ours was from a 58-year-old woman who had had two bouts of irradiation for vaginal bleeding. She continued to bleed and subsequently had a hysterectomy, revealing a firm yellow circumscribed 2 cm. tumor.

Here illustrated is a variety of pure theca-cell tumor showing the typical hyalinized bands and bundles of thecal stroma. It represents the ability of theca externa cells to lay down collagen and mimic the ability of this type of tissue to form corpora albicantia.

Here illustrated is a granulosa-cell carcinoma, not only histologically quite typical, but clinically malignant. The patient is still alive but is dying of generalized peritoneal carcinoma proved by cell block to be of granulosa-cell type.

Here illustrated is a case which shows some of the difficulties one gets into histologically in evaluating these tumors. It has been brilliantly brought out in this study by Anderson that there are differences of opinion. This particular case is listed in the files of the Free Hospital for Women as a granulosa-cell carcinoma. She did die from this lesion and I suspect that this folliculoid area over here is what made me call it granulosa-cell carcinoma, but you also find here some sort of tubular development or adenocarcinoma, and I think in all fairness that this is probably not a granulosa-cell carcinoma, although it is carcinoma of the ovary. Therefore, even though this is called granulosa-cell carcinoma in the files, it will be changed simply because morphologically it does not seem to have all the characteristic hallmarks we would like to see in a granulosa-cell carcinoma. Incidentally, her endometrium showed no evidence of estrogen stimulation.

In concluding my discussion of this very fine paper, I would like to point out that in our series of 43 cases at the Free Hospital for Women, the average distribution as to histologic types was as one might expect it to be: half of them were essentially pure or predominantly granulosa-cell tumors, and the other half were essentially pure thecomas. It is interesting to note that 75 per cent of these patients had irregular and profuse bleeding, often after the menopause, and that microscopically their endometria were normal in 21 per cent, showed cystic hyperplasia in 21 per cent, adenomatous in 9 per cent, and in 14 per cent there was anaplasia; there was carcinoma in situ morphologically malignant in 14 per cent; early definite adenocarcinoma in 7 per cent; and a true carcinoma that invaded the myometrium in 12 per cent.

In summary, the Committee, especially Dr. Novak and his devoted workers, and Dr. Anderson who has done the majority of the work in putting this paper together, are to be commended for tackling very large, important, and often very difficult group of tumors that are so important to the welfare of the patient.

DR. EMIL NOVAK, Baltimore, Md.—I can speak for the Ovarian Tumor Committee in expressing its gratification for this fine paper, which has been based on our Registry material. A good many papers have already been published utilizing this material, and there would seem to be no end to the possibilities along this line.

In the short summary Dr. Anderson could make, I think he was wise in limiting himself to one or two aspects, perhaps especially to the question of the degree of malignancy. The authors have for the first time tried to grade this group of tumors histologically. I consider this very important, this grading being correlated with the clinical history.

In the past there have been a number of misconceptions about granulosa-cell tumors. It has been so constantly said that they have a relatively low degree of malignancy that clinicians and pathologists take these tumors too lightly, because, as a matter of fact, they are sometimes very malignant. I recall a case in which radical surgery was done for such a tumor, and in which within three months the patient returned with extensive peritoneal recurrence. Of course, the majority of these mesenchymomas are of a low degree of malignancy, and recurrences are sometimes very slow. I remember that in the early days of our knowledge of this group of tumors I presented a paper on the subject before the International Congress of Carcinoma. When I got through, my paper was discussed by a man whom I consider one of the best pathologists in the country, Dr. Shields Warren. He said that he wondered why I had used the term granulosa-cell carcinoma, because, as he said, "all these tumors are benign." I am sure he does not think that now, but this comment gives you an idea of the thinking of many people in those days. It is of interest that in this early study of 32 cases (Novak and Brawner: AM. J. OBST. & GYNEC. **28**: 637, 1934) the recurrence rate was not far removed from that found by the present authors.

I have seen all the cases reported by the authors today. In going over this material and all sorts of other tumor material, one thing which has impressed me is that we should have good sections and plenty of them in order to evaluate them properly. One section Dr. Anderson showed today came from a rather degenerated area, and it will illustrate this point.

It seems to me that in their individual variations in malignancy, these mesenchymomas are somewhat like the serous papillary tumors. If a granulosal tumor, or a papillary tumor, is obviously highly malignant histologically it is almost surely clinically malignant as well. If such tumors, on the other hand, show very little anaplastic activity histologically, they are much less likely to recur or metastasize, but there are not infrequent exceptions.

DR. D. NELSON HENDERSON, Toronto, Canada.—At the Toronto General Hospital and the Ontario Institute of Radium Therapy we have had a large number of these tumors to study and follow—45 in all, and I thought it would be of some interest to make a comment in regard to our experience with these patients.

We have 12 patients with recurrent tumor; 7 developed their recurrent tumor within five years; 3 developed their recurrence between five and ten years, and 2 after a lapse of over ten years. In view of the report given this morning and the comments relative to the degree of malignancy being of prognostic value, it is further interesting to note that in our cases, 3 developed recurrent tumor after a passage of 5 years and those tumors were of a benign follicular variety. We have one tumor of the tubular variety which was markedly luteinized; this occurred in a child of 8 years who showed signs of precocious puberty. The tumor was removed but recurred in the other ovary four years later and eventually will lead to the death of the patient.

Of our 17 patients who lived over five years, 14 had bilateral oophorectomy and hysterectomy. What concerns us is this: when we encounter granulosa-cell neoplasm in a young woman, should we perform radical surgery? We have had one death in a child of 8 and in a young woman of 21 years. It is with reluctance that we perform bilateral oophorectomy and hysterectomy in a young patient. Should we, in this type of neoplasm, do this radical surgery?

DR. TRENT BUSBY, Salisbury, N. C. (By invitation).—I wish to show one slide to add a point about prognosis in this series. In the analysis of the 20 deaths within the five-year period of follow-up, 14 had extension of the tumor to the pelvis at the time of the original operation. The prognosis is poor because of the extension of the tumor and death of these patients was accounted for on the basis of this extension. There were 6 patients who died in the five-year period who had no extension of the tumor beyond the ovary; 2 of these had rupture of the tumor and the patients died of hemoperitoneum. The histologic grades of these tumors were I and II. There were 4 who died of metastases following excision of the tumor when it was limited to one ovary, but these were histologically Grades III and IV.

Thus it appears that, when the tumor is limited to the ovary and if the degree of histologic malignancy is low, the five-year expectancy for the patient is good.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—I wish to ask the authors if they have seen the development of a granulosa-cell tumor following complete irradiation therapy of cancer of the cervix in which the result from the irradiation treatment had been successful for ten years.

At that time, and in the same year, two such patients were operated upon at Jefferson Medical College Hospital because of abdominal tumors, both of which proved to be granulosa-cell tumors. At operation no evidence of residual cervical cancer was found. Both patients died several years later of cardiovascular disease, still with no evidence of recurrent malignancy.

DR. RICHARD W. Te LINDE, Baltimore, Md.—I wish to make one comment. The Fellows of this Society know how much discussion we have had about the value of the Ovarian Tumor Registry, and I think this paper is an excellent example of its merit. We are not through with these morphologic studies of ovarian tumors, and any study such as this adds a great deal to our knowledge. These are rare tumors, and where could you get an assembly of such tumors except in the Registry?

In regard to five-year cures of granulosa-cell tumors, that really means nothing. Dr. Jones and I reported three recurrences, 14, 16, and 20 years after the original tumor was removed. We had the original and final specimens in the laboratory and they were identical.

DR. GEORGE W. ANDERSON (Closing) (By invitation).—Dr. Hertig and I have had a number of interesting discussions which have been of benefit to me in illustrating that this is a tremendously difficult histologic exercise and that there are all kinds of differences of opinion, but out of these differences of opinion may come a proper and true knowledge of the nature of the tumor.

The value of grading in this problem is that it sifts out a group of very malignant-looking tumors based on histologic appearance in determining malignancy. Whether these tumors will remain in this same classification in the years to come I cannot predict. It would take an atlas to illustrate to you all the various tricks of these tumors. We had a gentleman's agreement to stay away from describing the normal types of tumors, and Dr. Hertig has illustrated some of these very interesting tumors in his large practice.

I did not have time to discuss treatment. Most of our deaths occurred in women over 50 years of age and of those there were 4 who had only simple oophorectomy. Under the age of 50 and in the childbearing age, I believe that if extension is proved beyond question of a doubt at the time of surgery, it would really be fielder's choice, but you could say on the basis of potential malignancy that complete exenteration should be done.

In answer to Dr. Scheffey's question, we have just 2 cases in the Registry and they followed irradiation.

We have gone into the delayed recurrence problem. The literature is loaded with cases of Grade I that have gone many years following their original surgery, but the frequency of recurrence is a sobering note in the prognosis for any woman with this type of tumor.

A paper of this type could not be possible without the cooperation of many people, and we wish to thank the Society for the privilege extended us.

DR. NORMAN MILLER, Ann Arbor, Mich.—Could we have a definition of "complete exenteration" from Dr. Anderson. For the purposes of the record this should be quite clear.

DR. ANDERSON.—I would classify that as oophorectomy, salpingectomy, and total hysterectomy.

ENDOMETRIOSIS PERITONEI—RELATIONSHIP OF PAIN TO FUNCTIONAL ACTIVITY*

SOMERS H. STURGIS, M.D., AND BARBARA J. CALL, M.D., BOSTON, MASS.

(From Peter Bent Brigham Hospital)

RECENTLY a fairly complete bibliography on endometriosis covering the last five years listed some 225 articles.[1] The probable explanation for such attention in the world literature is not only that this condition has been called "one of the more serious afflictions of modern woman"[2] but also that it still involves conflicting theories on etiology, and unresolved problems in management. The present contribution is not concerned with either of these areas of disagreement nor does it add further statistical data to an understanding of differential diagnosis or therapeutic results. The cause of pelvic pain, probably the commonest symptom first leading to the diagnosis, has not been extensively studied, however, and its relation to the dynamic physiology of the disease has been little appreciated. The failure to recognize this relationship has resulted in certain misleading concepts and has left us with some perplexing paradoxes. Part of the confusion stems directly from attempts to force all facets of this multiplex condition into a single mold. Yet there is grossly little clinical or pathologic similarity, for instance, between adenomyosis and a large "chocolate cyst" of the ovary. Although recognizing that such different manifestations of endometriosis are often concurrently present, we have arbitrarily chosen to limit this discussion to but one type of lesion—ectopic tissue arising in or from the pelvic peritoneum. By thus simplifying the problem, it becomes easier to spell out a reasonable explanation for some of the puzzling features of the disease. Sample abstracts and photomicrographs have been selected† to illustrate a sequence of events correlating pain with the developmental activity of endometriosis peritonei.

To those familiar with the condition there is little need for extensive description of the characteristic dark "blueberry spots" which are never more than a few millimeters in diameter and, of course, represent tiny collections of old blood pigment in areas that generally show microscopically recognizable ectopic endometrium. It has been casually assumed that the classic association in the uterus itself of cyclic endometrial breakdown and bleeding also no doubt occurs in similar but ectopic endometrial fragments, and that such miniature menses into blind pockets readily explain the clinical incidence of periodic pelvic pain. This simple but in large part erroneous explanation is responsible, we believe, for several areas of misunderstanding.

*Presented by invitation at the Seventy-seventh Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 20, 21, and 22, 1954.

†We are grateful to Dr. J. V. Meigs, not only for his interest and sympathetic encouragement, but also for permission to include selected cases from his practice among the forty-six protocols that were studied as the basis for this report.

First, surgeons are all familiar with the rapid spread of subserosal hemorrhage from an uncontrolled bleeding point in the course of pelvic operations. Why, then, if ectopic menstruation occurs once a month in endometrial fragments, is there never found a widely extended area of subperitoneal discoloration about these lesions?

Second, next to the characteristic dark spot of central discoloration, the most typical feature of endometriosis peritonei is the white, tough scar tissue surrounding each lesion, and extending radially outward over the peritoneum as well as deeply into the structures beneath. These fibrotic fingers often involve and infiltrate the surface of any contiguous organ—the ovary, tube, rectosigmoid, or small bowel, and have given rise to the idea that endometriosis itself is an "invasive" growth. Why is it not possible then always to demonstrate under the microscope specific endometrium at the periphery of these scarred areas?

Third, although the onset of periodic pain in the fourth decade is the most characteristic complaint suggesting the diagnosis, and the palpation of firm, irregular nodules in the cul-de-sac is the commonest confirmatory preoperative finding, why does the pathologic picture show so often a minimum of specific tissue in excised lesions?

Fourth, if ectopic menstruation into blind pockets causes pain, how best explain the reported incidence of the disease showing a peak at age over 30, at least 15 years, or an average of more than 200 menses, after the menarche?

Finally, if bleeding in these displaced endometrial fragments results from their active response to ovarian hormones, and pain is a consequence of such activity, how can one explain the frequent remission of symptoms and apparent resolution of palpable areas under the excessive hormone drive of pregnancy or under treatment with massive and prolonged doses of estrogen?

The answers to some of these questions may be found in an appreciation of the dual nature of the disease process. It is important to recognize not only a diversity of differentiation of ectopic glands and stroma with a corresponding variation in response to hormonal stimuli, but equally a varied reaction of the host tissue bed in direct relationship to the activity aroused by such hormonal response.

For purposes of clarification one may recognize three stages in the life cycle of peritoneal endometriosis. The first involves etiology, and whether this is a matter of surface implantation or of metaplasia or of lymphatic or blood-borne metastases, it will not be further discussed here.

The second is the active stage of the disease with which the present discussion is concerned.

The third stage is that of relatively symptom-free postmenopausal inactivity. It must be emphasized once more that there are, commonly, multiple pathologic foci, and further, that it is difficult indeed to obtain proof that any single lesion may have been the cause for pain in a given case. Yet it seems probable that activity in the epithelial glands and stroma of ectopic endometrium sets up the same type of reaction in the surrounding tissues as

any irritant foreign agent. Such a "foreign body reaction" is one of proliferation of fibroblasts and the deposition of inelastic scar tissue as an attempt to infiltrate, block off, and delimit the areas of irritant activity. When, toward the end of a menstrual cycle, there is a withdrawal of circulating ovarian steroid, then a regression of activity in the lesions takes place. The accumulation of secretory debris with a certain amount of degenerated cellular elements in these areas provides a further irritant focus in the host tissues. It is probable, however, that desquamation, necrosis, and gross escape of blood as are the rule in the uterine endometrium rarely occur in ectopic lesions. This may be explained by the fact that the mechanism of endometrial breakdown in the uterus depends upon the complicated and unique arrangement of spiral arteries that grow out each month to nourish the superficial endometrium. It is extremely unusual to demonstrate the presence of spiral vessels in the stroma of endometriosis involving peritoneal surfaces. Yet more than 25 years ago Novak[3] recognized that gross hemorrhage from the endometrial surface is not the only type of blood loss in the menstrual cycle, and Markee[4] described five mechanisms whereby blood escaped from the vascular tree in anterior chamber transplants. One of these appears to be an extravasation of erythrocytes due to diapedesis of individual blood cells through the capillary walls. Such a process well may account in good part for microscopic amounts of bleeding into the stroma surrounding ectopic epithelial glands. The red cells probably become phagocytized as suggested by Sampson,[5] but the changed blood pigments remain in situ or gradually accumulate to form the tiny subserosal collections with characteristic "chocolate" color that signify the "blueberry spots" in the pelvis.

As suggested previously, the monthly response in endometriotic areas will vary all the way from a minimum activity similar to that seen in the basal layer of uterine endometrium to the maximum that occurs in the compact and spongy layers. Where this response has been maximal, there one would expect an equally aggressive deposition of surrounding fibroblasts. Cyclic edema fluid collection, extravasation of blood cells, and cellular and secretory debris all tend to expand and enlarge the area, while commensurate reparative processes are called forth in the host to encapsulate, infiltrate, and organize each irritable focus with scar tissue. Eventually, in many cases, this host reaction successfully encapsulates and then gradually but ultimately completely replaces the specific endometrial structures with solid fibrosis. At other times, due to more fully differentiated structures, or more powerful or prolonged hormonal stimuli, or perhaps a less effective fibrous response in the host, the endometriosis tissue may continue to grow and expand and survive beyond the function of the ovaries and even into the postmenopausal era.

Perhaps chief among the factors that define whether or not fibrotic encapsulation will occur is the relation of ectopic endometria to the serous surface of the peritoneum. Those lesions directly beneath or on the surface may expand outward, bulging into the peritoneal cavity, and never become

bound by a fibrous wall. On the other hand, lesions buried deeply below the surface more likely call forth an enveloping response. This may be the most important aspect of the disease that determines whether or not there will be

Fig. 1.

Fig. 2.

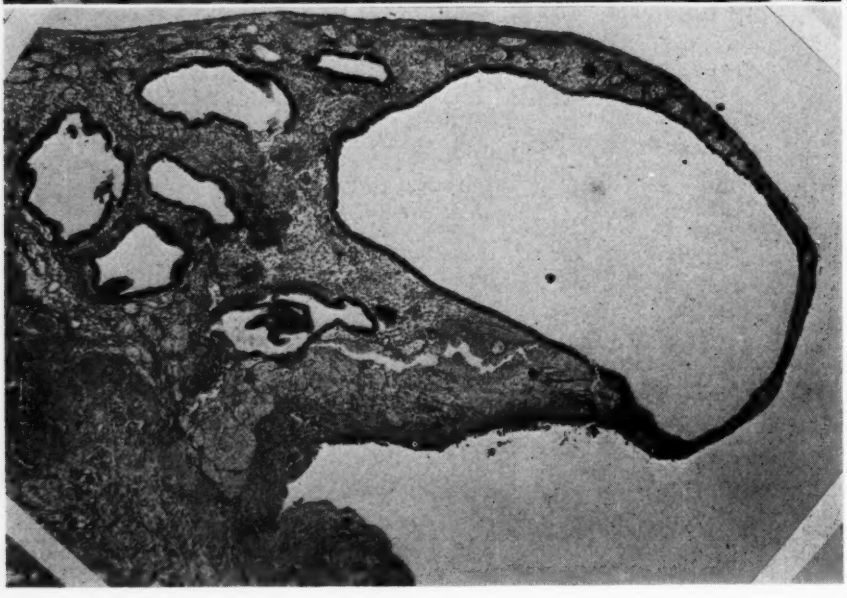


Fig. 1.—Case No. 7452. Lesion from uterosacral area showing active proliferative response in a 36-year-old single woman operated on for leiomyoma. This tissue is superficial, bulges outward from the surface. No history of pain.

Fig. 2.—Case No. 7623. Lesion from right uterosacral ligament removed on cycle day 27 of a 43-year-old single woman operated on for fibroids. This endometrial tissue with cystic glands protrudes in a polypoid fashion from the serosal surface. The stroma is edematous. Under higher power, subnuclear vacuoles can be seen in places in the epithelium. The tissue is responding to progesterone. The patient gave no story of pelvic pain.

periodic pelvic pain (Figs. 1, 2, 3, and 4). Whenever a lesion becomes firmly bound within a fibrotic wall, however, but still maintains functional activity each month, then the expansile nature of this response within unyielding scar causes increased pressure and thus pain (Figs. 5, 6, 7). It may well take

Fig. 3.

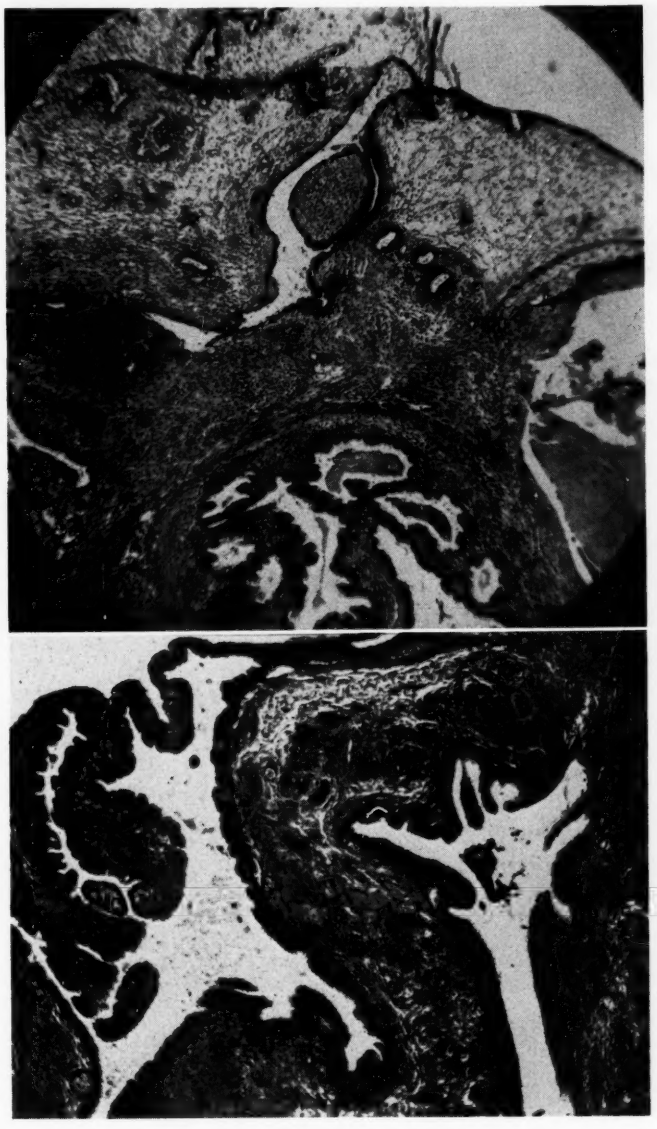


Fig. 4.

Fig. 3.—Case No. 8109. Area excised from uterosacral ligaments in a 42-year-old single woman operated on for fibroids on the twentieth day of her cycle. The superficial endometrial stroma is edematous and the glands beneath show a typical secretory pattern. The lesion is actively responding, and bulges from the peritoneal surface. There was no complaint of pain.

Fig. 4.—Case No. S-53-1773. A 37-year-old para iv admitted for metrorrhagia and hysterectomy performed for fibroids. This area was a bluish, puckered lesion located on the anterior bladder flap. The endometrial tissue lay directly beneath the surface, showed stromal edema and a typical secretory phase of epithelial glands. The patient had worn a brace for backache for one year, but had no cyclic or menstrual pelvic pain.

years of menstrual irritation to call forth such a fibrotic capsule. Gradually, the lesion becomes strangled by fibrous organization, yet, while there are still specific structures capable of stimulation, even though almost entirely replaced, then there will still be the elements necessary to explain periodic pain.

With such a concept in mind of a tug of war between the ectopic lesion responding up to its capacity as endometrium and the tissue bed of the host reacting with limiting fibrosis, let us attempt an answer to the perplexing questions previously given.

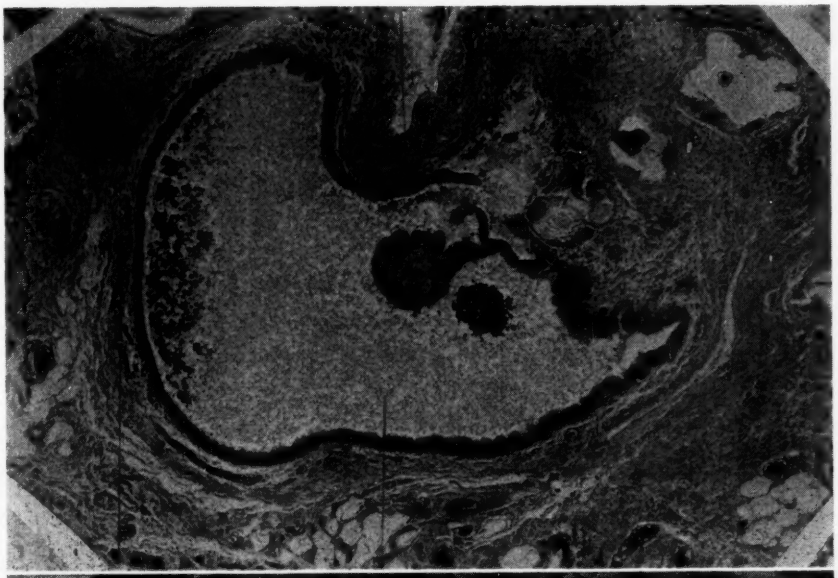
First, it is probable that endometrium displaced onto or under the peritoneum rarely attains sufficient differentiation to develop the special spiral arteriolar pattern essential for true menstrual desquamation and hemorrhage. Not only is there probably only minor diapedesis into the stroma, but such as does occur will be prevented from spreading as a subserosal hematoma by the surrounding scar tissue. Therefore, one would not expect to encounter gross evidence of fresh blood even when operating at the time of uterine flow.

Fig. 5.—Case No. S-47-1867. A 32-year-old para ii, who complained of pain increasing progressively from a few days after menses to the next flow and who presented palpable nodularity in the cul-de-sac. This area from the pouch of Douglas shows an endometrial gland deep beneath the surface enveloped in a fibrous wall. The patient had typical cyclic pelvic pain.

Second, the radial expansion of fibrosis about a lesion is not a centrifugal invasion by the endometrium itself into surrounding organs and structures, but rather an exhibition of a widely recognized foreign-body reaction called forth by the irritant nature of the central, active areas. The adhesions are built up by the contiguous host tissues, and are not due to any invasive or infiltrative faculty of the endometrium itself.

Third, it is probable that at times cyclic response in ectopic areas may take place month after month for years before, gradually and inevitably, sufficient fibrosis is called forth to hamper and restrain the elements that

Fig. 6.



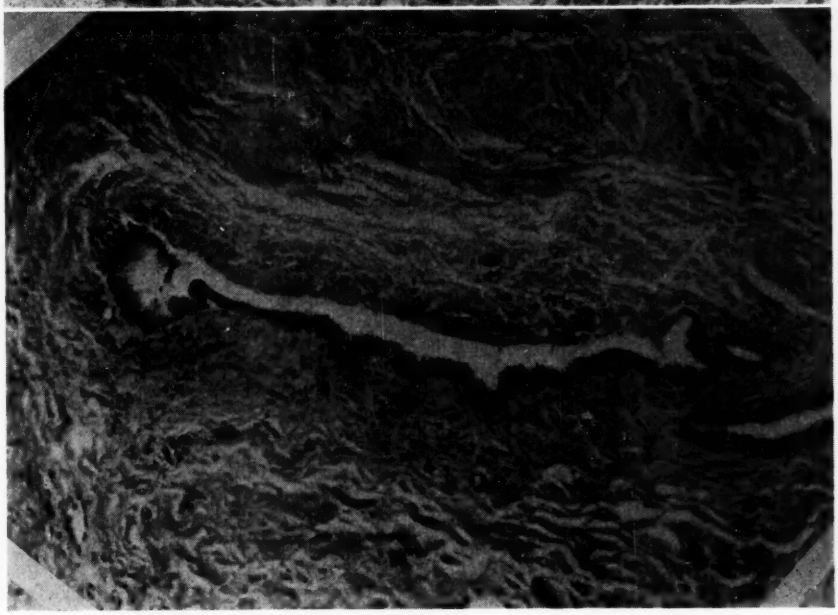


Fig. 7.

Fig. 6.—Case No. 7766. Area from the uterosacral ligament in a 44-year-old nullipara operated upon for discomfort from midinterval to onset of menses for four years. The uterus was retroverted and fixed with nodularity behind the cervix. A single cystic structure was seen containing blood cells and debris. A minimum of recognizable stroma was found. These structures were well beneath the surface and surrounded by an envelope of firm fibrous tissue. Monthly pain was present.

Fig. 7.—Case No. 6847. A 30-year-old nullipara with severe and cyclic backache, who showed a retroverted and fixed uterus. This lesion from the right uterosacral area was grossly typical of endometriosis. A narrow cystic structure was seen embedded within a block of fibrous tissue. There was no recognizable endometrial stroma. Some of the epithelial lining was lost. Yet, this patient had monthly pain.

tend to produce swelling, expansion, and pain. This would not occur readily in lesions that might bulge into the abdominal cavity from the surface. The deeper lesions, on the other hand, already may be expected to show a considerable degree of replacement and organization by scar by the time that monthly pain is sufficient to bring the patient to her doctor. By this time,

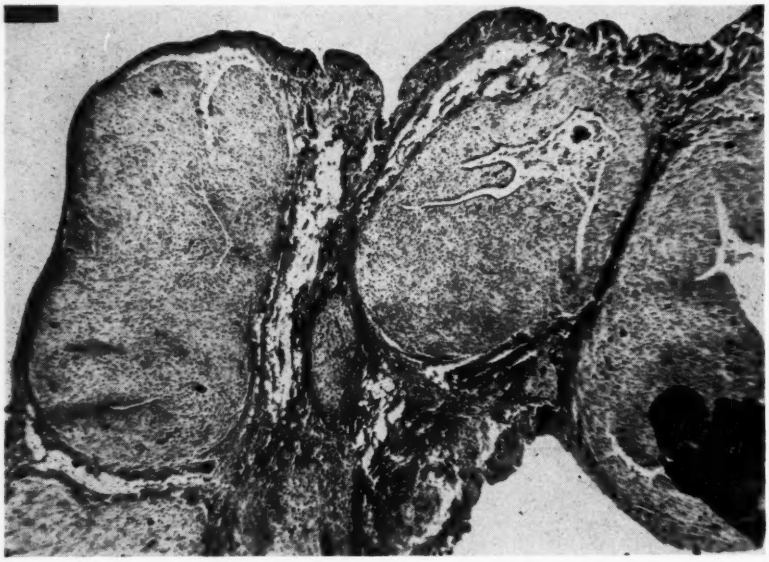


Fig. 8.—Nodules of subserosal deciduomas removed at cesarean section from the peritoneal surface. It is postulated that these differentiated from endometriosis peritonei due to the stimulus of pregnancy levels of ovarian steroids. Such lesions would be too soft to palpate and associated with remission from pain during pregnancy.

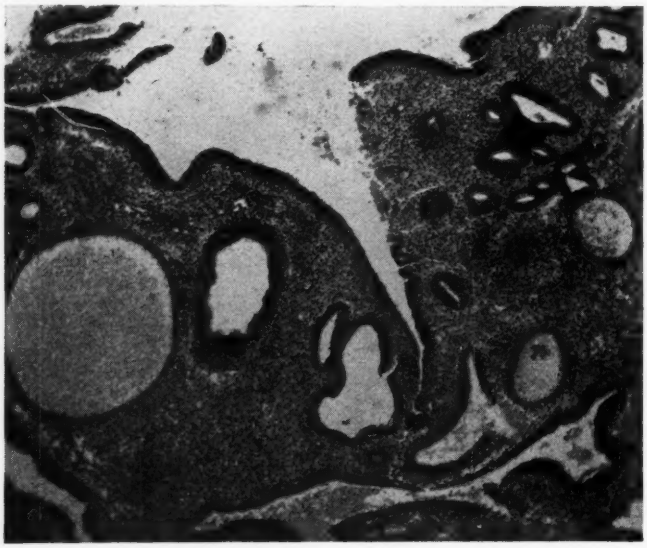


Fig. 9.—Case No. S-52-533. Endometrial biopsy in a 34-year-old nullipara after she received approximately 4,000 mg. of Des-stilbestrol over five months for postoperative recurrence of pelvic pain associated with widespread endometriosis. This tissue is responding with exuberant anaplasia and hyperplasia. The patient was relieved of pain after the first six weeks of treatment.

therefore, there may well be only a minimal amount of pathologically recognizable specific structure deeply embedded in scar. Only such heavy fibrosis is easily palpated as nodular thickening in the posterior cul-de-sac. It is in the latter phase of the second stage of the disease, when the endometriosis itself is almost burnt out, that the diagnosis is most readily made before operation. This explains why the peak incidence is reported as between 30 and 40 years. This is not at all the incidence of origination of the disorder; it reflects the incidence of diagnosis made possible by the passage of years and the accumulation of unyielding scar.

Finally, when pregnancy provides an overpowering stimulus to endometrial growth and differentiation, then these ectopic areas may break through any encapsulating bonds and expand luxuriantly over the peritoneal surface. These soft, decidual masses are then no longer palpable (Fig. 8). Similarly, it is likely that prolonged and massive estrogen dosage produces an abundant and uncontrollable hyperplasia in ectopic areas as it does in the uterine endometrium (Fig. 9). Physical examination will then show a misleading "resolution" of previously hard and fibrotic areas.

Conclusions

In conclusion, it may be postulated that pain is most often associated with a terminal phase of fibrosis in the waning function of endometriosis peritonei. The apparent invasive characteristic of this disease is explained as a secondary metaplasia of the host connective tissue into adherent scar. It follows that in the surgical extirpation of these lesions, it should be necessary only to eliminate the reactive foci and not necessarily the whole area of scar. If by simple cauterization one could surely destroy all potentially reactive areas, then the relatively mutilating operations designed to remove widely the whole peritoneum of the cul-de-sac would not be necessary to control the cyclic pelvic discomfort that so often may be the major reason for any therapeutic measure.

This is a presentation of a concept of the active stage in the life cycle of endometriosis peritonei. The multiple lesions so frequently encountered in any given case probably will show major variations in differentiation and reactivity, and it is almost impossible therefore to obtain statistical data to prove the relationship of any single area to monthly pain. The conclusion that only the centrally responding tissue need be extirpated is unfortunately of more theoretical than practical value, since one cannot recognize grossly wherein may lie microscopic nests of specific glands or stroma in widespread scar. Nevertheless, the considerations here defined appear to suggest acceptable explanations for some of the otherwise puzzling clinical aspects of this common and painfully disabling disease process.

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Discussion

DR. JEAN PRATT, Detroit, Mich.—The quandaries about endometriosis are truly amazing when one considers that the condition was discovered more than a century ago. In spite of much investigation and discussion, the etiology, diagnosis, and treatment remain an open subject. The essayist, well aware of the perplexity, has focused his attention upon a particular phase of the subject and has proposed an ingenious theory to explain the cause of pain in endometriosis arising in or from the pelvic peritoneum.

Acceptance of his statement that pelvic pain is probably the commonest symptom first leading to the diagnosis of endometriosis of the peritoneum may be misleading unless qualified. It might be inferred that most endometriosis causes pain. On the contrary, most of the lesions do not cause any symptoms. At operation endometriosis is often discovered incidentally and no symptoms referable to the lesion have been noted before operation. Inquiry of the patient after operation discloses no such symptoms that could be explained by endometriosis. Furthermore, during routine pelvic examinations as a part of general physical examinations, characteristic "shotty" nodules are frequently noted in the pelvis, especially on the uterosacral ligaments. Enough of these have been checked at operations which were performed for other conditions to give confidence that these lesions can be diagnosed routinely with a reasonable degree of accuracy. Most of the lesions give no symptoms.

The degree of pain does not necessarily bear any direct relationship to the amount of endometriosis present. This observation is in keeping with the authors' emphasis placed upon recognizing "not only a diversity of differentiation of ectopic glands and stroma with a corresponding variation in response to hormonal stimuli, but equally a varied reaction of the host tissue bed in direct relationship to the activity aroused by such hormonal response."

The host tissue may respond to a variety of stimuli. Hence, peritoneal endometriosis does not produce any pain which is absolutely characteristic or which cannot at times be produced by other pelvic lesions.

Endometriosis has been repeatedly described as developing gradually over a period of years. Has this been established by factual evidence or has it been assumed? I have followed a number of patients for years without observing any appreciable increase in the extent of the lesions. Whatever the etiology it seems likely that many of the lesions occur as a single episode, probably early in the reproductive years and remain in the same condition indefinitely. With each cycle, however, there is a temporary rise and fall in response to the steroid stimulation. There is wide individual variation in the response. The individual variation is similar to that of premenstrual tension. Although menstrual histories are comparable among women in the reproductive age, not 50 per cent are aware of premenstrual tension, yet the ovarian hormones are sufficient to produce regular menstrual cycles. In both instances the emotional stability and sensitivity to pain, as well as the local lesion, are important factors.

That the pain in endometriosis is dependent upon ovarian function is generally accepted. Only the manner in which the pain is produced is questioned. If the pain is inherent in the endometriosis nerves capable of responding to and transmitting the impulse should exist. Has anyone ever demonstrated nerves in endometriosis? If this is a foreign-body reaction, is it logical to assume that nerves grow into the lesion? The theory that the pain caused by pelvic endometriosis originates in the host tissue is supported by the lack of evidence that pain can originate in the lesion.

Interpretation of the mechanism of pain in the host tissue should include recognition of the varying sensitivity of the pelvic organs and tissues in different phases of the cycle. As menstruation approaches, the majority of women feel at least a sense of weight and pressure in the pelvis. All degrees of discomfort from simple sensitivity to severe pain and tenderness may be found in different individuals and sometimes at different times

in the same individual. A parallel may be seen between the degree of sensitivity and the amount of pain when endometriosis is present. Would this explain why of two lesions that seem the same on examination one is tender and painful and the other is not?

DR. STURGIS (Closing) (By invitation).—It is true that pain is not a common feature and that a great many cases of peritoneal endometriosis are found at operation without any warning of pain beforehand. It would take a lot of statistical data to get enough cases to show that these may be the ones where the lesions are on the surface of the peritoneum. Even though scar tissue is laid down at their base, this would not confine them so there would be no pain, but still they might be palpable.

(The papers of Drs. Allen, Sherman, and Arneson, and of Dr. Fluhmann presented at this meeting will be published in the December issue.)

Item

American Board of Obstetrics and Gynecology

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities of the United States, Canada, and military centers outside the continental United States, on Friday, Feb. 4, 1955.

Case Abstracts numbering 20 are to be sent by the candidate to the Secretary as soon as possible after receiving notification of eligibility to the Part I written examination.

Candidates are reminded at this time that lists of hospital admissions must accompany new applications and requests for reopening.

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